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Food as medicine? Exploring the impact of providing healthy foods on adherence and clinical and economic outcomes

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ABSTRACT

Background: Chronic disease prevalence is increasing. Adherence to dietary guidelines is low (<50%) despite positive impacts in disease progression, clinical outcomes, and medical costs. It is important to summarize the impact of providing medically-tailored meals to patients on adherence rates, clinical outcomes, and potential economic outcomes.
Methods: A systematic review was conducted to identify, extract, and appraise food-provision studies from January 1, 2013-May 1, 2018 for heart disease, diabetes (DM), and chronic kidney disease (CKD). The key findings related to adherence and clinical outcomes were compiled. Published literature was utilized to determine the economic impact of key clinical outcomes.
Results: Across diseases, 100 articles ($N = 43{,}175$ patients) were included. Dietary adherence was considered "compliant" or ≥ 90% consistently. Significant ($p < 0.05$) clinical outcomes included 5–10% LDL reduction, 4-11 mmHg SBP reduction, 30% reduction in metabolic syndrome prevalence, 3–5% weight reduction, 56% lower CKD mortality rates, and increased dialysis-free time (2 years:50%, 5 years:25%, calculated cost savings of 80.6–94.3%). Literature review showed these outcomes would result in decreased: cardiovascular (CV) event risk (20–30% reduction: $5–11 billion annually), hospitalization costs ($1–8 billion), and dialysis rates (25–50% reduction: $14–29 billion annually). For heart failure patients, results include: 16% fewer readmissions (saving $234,096 per 100 patients) and a 38-day shorter length of stay (saving $79,425 per hospitalization).
Conclusion: Providing medically-tailored meals significantly increases dietary adherence above 90% and allows patients to realize significantly better chronic disease control. Through this, patients could experience fewer complications (CV events, hospital readmissions and dialysis), resulting in significant annual US healthcare cost reduction of $27–48 billion.

1. Introduction

It is crucial to address the risk factors and modifiers associated with chronic disease to improve outcomes for patients and employers while also lowering the heavy costs of healthcare. Healthcare costs continue to rise in the United States, with $3.3 trillion spent in 2016. Projections for future spending estimate an average growth rate of 5.5% annually.[1] Most spending occurs in working-age adults (54%), while the healthcare spending is three times higher in older adults (≥65 years).[1] According to the Center for Disease Control (CDC), 86% of healthcare spending is for patients with chronic disease and mental health conditions, such as heart disease, diabetes, and chronic kidney disease (CKD).[2] Because a bulk of this healthcare spend is associated with chronic disease, finding affordable methods for addressing chronic disease management is essential.

Additionally, these chronic diseases are the leading causes and contributors of morbidity and mortality in adults. For example, heart disease and stroke are the leading causes of death (one-third of all deaths) with over 868,000 Americans dying each year.[2] In addition, over 100 million US adults have prediabetes or diabetes,[2] which places them at risk for heart disease, chronic kidney disease, and vision loss. These diseases not only have impact in terms of mortality, but they produce significant morbidity, leading to a loss in work productivity and significant healthcare costs. Heart disease and diabetes alone cost employers and the healthcare system over $550 billion annually, particularly due to high hospitalization and readmission rates, which can contribute up to 61% of costs.[2–4]

Important risk factors to address include: obesity, lack of dietary adherence, lack of physical activity, and smoking. Two out of every three adults are overweight or obese (70.7%),[5,6] and this contributes significantly to the

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rising healthcare costs and places patients at risk for heart disease and diabetes.[2] Patients who are overweight or obese, with or without chronic disease, cost $3559 more annually in per-patient medical expenditures.[5] This becomes even more concerning when patients already have existing chronic conditions, such as heart disease and diabetes, that are exacerbated by obesity. For example, the healthcare costs of diabetic patients are 2.3 times higher than patients without diabetes, and approximately $9600 annually per patient is attributed to treatment and management of diabetes.[7]

Because of the effect diet can have on chronic disease, patients are often asked to adhere to a disease-specific diet via lifestyle interventions. Clinical practice guideline recommendations for preventing and treating obesity,[5] heart disease,[8,9] diabetes,[10,11] and chronic kidney disease[12] serve to address obesity and prevent or modify the risks of chronic disease. Further, in geriatrics, the nutritional needs of older adults are especially critical where approximately 10% of older adults live alone and nearly 60% in long-term care are undernourished.[13] In this patient population, comorbid obesity is prominent due to low nutrient-density, sugary, and processed meals.[14] It is well-documented in the literature that patients adhere to their dietary regimens less than 50% of the time.[15,16] There are multiple reasons for low adherence including diet complexity,[15] challenges integrating into their daily lives,[10] literacy issues of reading labels,[17] and uncertainty about eliminating preferred foods.[16] If patients become adherent and attain healthy weights, there is potential for substantial cost savings related to improved overall health outcomes and decreased hospitalizations. For example, in diabetes, an intervention that would assist patients in becoming adherent to dietary changes could result in a minimum of $75 billion annually in savings (30 million diabetics, assuming 70% of patients are overweight or obese, and $3559[5] greater annual spending). Actual cost savings are likely higher due to the prevention of complications.

Culinary medicine provides medically-tailored meals which integrates evidence-based medicine and nutrition to create diet recommendations in which to prevent and assist patients with medical conditions.[18] Instead of finding the perfect one-size-fits all diet (which is problematic for many patients),[15,16] culinary medicine instead adapts to the individual patient's food preferences and disease states in order to improve health outcomes and prevent progression of disease.[18] Once the health care provider determines the patient needs, (s)he can then work with the patient to prescribe the best diet to accomplish mutual goals.[18] Investing in a prescribed/recommended diet is likely to be more beneficial for insurers, employers, and other payers, as preventing the complications and comorbidities associated with obesity and disease progression could result in significant cost savings. For example, a diabetes prevention program that costs $450 per participant could result in as much as $35,000 in annual individual savings.[19,20] These cost savings can even be more substantial, as reducing sodium intake could save $26.2 billion annually.[21,115]

Thus, the goal of this systematic review is to assess the impact of providing focused nutritional interventions on health, clinical and economic outcomes with the intent to form recommendations that combine evidence-based literature with best clinical practices. The objective of this project was to identify the potential economic impact of culinary medicine, where patients receive ready-to-eat meals medically-tailored to their specific disease state (according to nationally published guidelines), as well as related outcomes data on dietary adherence and health outcomes for patients with heart disease, diabetes (DM), and chronic kidney disease (CKD). The authors hope to compare the improvements in health related to these nutritional interventions with the known costs of chronic disease and establish utility of these interventions as a result.

2. Methods

A systematic review was conducted according to the PRISMA statement,[22] and the study protocol was generated prior to implementation and registered (PROSPERO CRD42019116570).[23] The literature was systematically searched for articles where food was provided in part or whole (in person or through free access) and reviewed. All reviewers (student research assistants, fellows, and faculty) were trained on the protocol prior to beginning.

2.1. Search strategy and study selection criteria

A thorough search of electronic databases was performed to ensure all relevant studies were collected for analysis. The databases searched were: Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Central Register of Controlled Trials, Health Source (Nursing and Academic Edition), Medical Literature Analysis and Retrieval System Online (MEDLINE), and PubMed from January 1, 2013 to May 1, 2018. In the initial pilot, a 10-year span was utilized. However, the volume of articles retrieved was too great; thus, the protocol was modified to include a 5-year span.

Study selection was not limited to any particular geographic location. Full text articles were required over abstracts due to the desire for a comprehensive integration of all accessible data. The researchers obtained any full text articles when accessible. Secondary screenings were performed on the references of studies to identify additional studies for inclusion. Only non-qualitative, primary literature was included.

Electronic search terms were generated through examination of the Medical Subject Headings (MeSH) in PubMed. Once a list of potential search terms was developed, the researchers ran trial searches in the electronic databases listed above. Table 1 includes the search terms with optimal results based upon number of articles and relevance. The nutrition terms in the first column of Table 1 were searched with each of the terms in the 5 topic areas in columns 2–6.

2.2. Eligibility criteria

After searching, potential articles were screened for eligibility. Inclusion criteria were: (1) topic of interest (diabetes, heart – heart failure (HF) or hypertension (HTN), geriatrics, kidney disease, and neurology – cognition), (2) participants 18 years of age or older, (3) dietary intervention that fit with clinical guideline recommendations, and (4) meals or meal items were provided to participants at some stage of the study. The fourth eligibility item was added to determine whether culinary medicine could be of value clinically and/or economically due to less variation in patient ability to adhere. Articles also had to be in English, be published in peer-reviewed journals within the last 5 years, contain non-qualitative research data, and be available in full text.

Table 1
Search terms.

Culinary Medicine Term	Geriatrics	Kidney Disease	Neurology	Diabetes	Heart Disease
Diet, Nutrition Therapy	Geriatrics, Aging, Frail Elderly	Chronic Kidney Disease, Dialysis, Kidney Function Tests, Kidney Disease	Parkinson's Disease, Alzheimer's Disease, Dementia, Neurology	Diabetes Mellitus, Diabetes Mellitus + Obesity, Ketoacidosis, Hyperglycemia	Heart Disease, Cardiovascular Function, Heart Failure (Diastolic), Heart Failure (Systolic), Hypertension

2.3. Data extraction

Two reviewers independently examined relevant articles to determine eligibility, and a final list of articles for each topic was compiled. If there were disagreements or questions about whether an article was eligible, one author (AC) resolved discrepancies. The final article underwent data extraction to identify: duration of intervention, dietary change implemented, assessment of intervention, and findings. The data extraction items were adapted from the process outlined in the *Handbook of Clinical Nutrition and Aging* on nutrition systematic reviews.[24] Per the protocol adapted for this review, authors were not contacted for further information in articles with partial selection criteria; rather, they were excluded from the study.

2.4. Bias and study quality assessment

All studies meeting the inclusion criteria were appraised in order to assess quality and potential bias. Two reviewers independently appraised each article using a dietary outcome tool from Lichtenstein.[24] The tool includes an appraisal of: methodological quality, applicability, and overall effect. Table 8 showcases the final result of each article graded in each of the aforementioned three categories using a scoring system described in Table 8's key. Methodological quality focused on overall bias, applicability focused on target population and generalizability to a wide group, and overall effect was specifically targeted to assess clinical benefit vs. harmful effects. Any disagreements or discrepancies were resolved by a third reviewer (AC). For each topic of interest, one author (JD) randomly selected 5 studies and independently appraised them to ensure consistency and quality of the appraisal process.

2.5. Pilot test

The systematic review protocol was pilot-tested with the topic of heart disease to identify any issues with the protocol itself or protocol implementation. The research team had originally planned to pull all dietary interventions, not only ones with meals provided. They also had planned for a 10-year span of studies. However, due to the sheer volume of studies, a fourth (meals provided) and fifth (heart disease limited to the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets) eligibility items were established and the span was limited to 5 years. At the completion of the pilot, the protocol was finalized.

2.6. Data management

All items pertaining to the systematic review were compiled and saved in a Google Team Drive folder. Google Forms that auto-populated Google

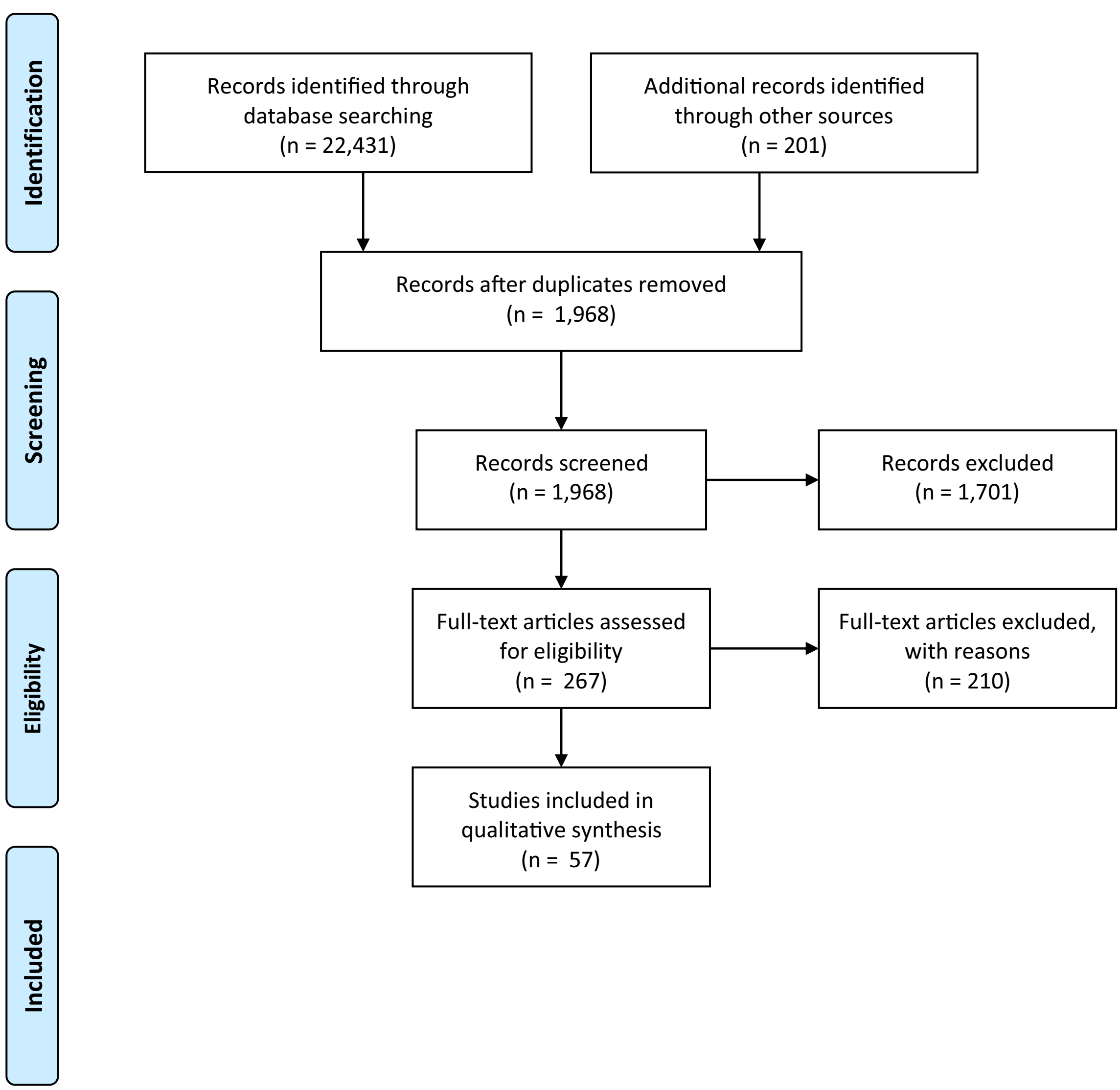

Fig. 1. PRISMA flow diagram.

Table 2
Article summaries of low carbohydrate and low caloric diets in diabetes.

Author (Year)	N	Study Length	Diet Assignments	Outcomes Assessed	Adherence/Compliance	Key Findings
Camps (2017)[69]	N = 11 Asian men	2 days	1 day on a high glycemic diet 1 day on a low glycemic diet	24-h glucose iAUC Fat oxidation	100%	Low vs high glycemic diet: • Lower iAUC (860 ± 440 vs 1329 ± 614 mmol/L.min)Greater fat oxication (0.043 ± 0.021 vs 0.034 ± 0.017)
Farrer (2014)[64]	N = 26 obese patients	12 weeks	Randomized to: • Very low-calorie diet (VLCD) with meals provided (participants covered the costs) • Calorie-deficit diet plan (control) Included traditional DM and weight loss education	Weight A1c Cholesterol	5/17 withdrew in control 2/9 withdrew in treatment Similar rates	VLCD vs control: • Greater A1c reduction (-1.5 ± 14.9 vs. -0.16 ± 7.4, $p = 0.017$) • Greater weight loss (6.6 ± 5.1 kg vs. 1.8 ± 2.6 kg, p = 0.004) • Greater BMI reduction (-2.3 ± 1.7 kg/m^2 vs. 0 ± 0 kg/m^2, $p < 0.001$)No significant changes in cholesterol
Goday (2016)[50]	$N = 89$ men and women Type II DM, BMI 30–35 kg/m^2	4 months	Randomized to: • Very low-calorie-ketogenic diet (VLCK, <50 g carbohydrates daily) – provided to participants • Low-calorie diet (control)	Weight A1c Cholesterol	Similar rates (Eating Self-Efficacy Scale) 92.5% rates the VLCK diet as satisfactory vs 68.5% control ($p = 0.005$)	VLCK had significant reductions in: • A1c from baseline: -0.9% ($p < 0.0001$) • Patients with A1c ≥7%: 46.7% to 12.8% ($p < 0.0001$) • BMI from baseline (33.3 ± 1.5 kg/m^2 to 27.9 ± 1.8 kg/m^2, $p < 0.001$) • Waist circumference (108.1 ± 8.6 cm to 96.1 ± 7.6 cm; p < 0.001) • TG from baseline (150.5 ± 54.4 mg/dL to 114.6 ± 57.2 mg/dL, $p = 0.0040$)VLCK: 97.6% lost >5% body weight and 85.4% >10% (<0.0001)
Gower (2015)[70]	$N = 69$ overweight/ obese men and women (incl. AA) N = 30 women with PCOS	16 weeks	Randomized to: • Low fat • Low carbohydrate8 weeks eucaloric 8 weeks hypocaloric Crossover randomized to: • Low fat • Low carbohydrate8 weeks on diet 1 then washout then 8 weeks on diet 2	Body composition Glucose metabolism	Compliant	Low carbohydrate vs. low fat: • Lost more fat tissue (11 ± 3% vs. 1 ± 3%; $p < 0.05$) • Lost 4.4% total fat mass • AA lost more fat mass (6.2 vs. 2.9 kg; p < 0.01) Low carbohydrate: • Decreased fasting insulin (-2.8 μIU/mL, p < 0.001) • Decreased fasting glucose (-4.7 mg/dL, p < 0.01) • Increased insulin sensitivity (p < 0.05) • Lost intra-abdominal fat (-4.8 cm^2, $p < 0.01$) • Lost intermuscular fat (-1.2 cm^2, p < 0.01)
Gu (2013)[71]	N = 45 healthy, obese $N = 30$ healthy, non-obese control	8 weeks	Very low carbohydrate diet (VLCD)	BMI Glucose metabolism	Compliant	VLCD in obese patients reduced (at weeks 4 and 8): • BMI from 32.58 kg/m^2 to 29.88 kg/m^2 (p < 0.01) • Fasting insulin ($p < 0.05$) • 2-h postprandial insulin (p < 0.05)
Tay (2014)[52]	$N = 115$ obese, Type II DM patients	12 weeks meals provided 12 weeks (Tay) to 44 weeks (Brinkworth) on own diet with key foods provided or voucher	Randomized to: • Hypocaloric low-carbohydrate, high--unsaturated/low-saturated fat diet (LC) • Energy-matched, high-unrefined carbohydrate, low-fat diet (HC) Included exercise program	A1c Glycemic variability Antiglycemic medication changes Lipids BP Weight Adherence	High compliance for both groups	LC vs HC: • Weight loss (-12.0 ± 6.3 kg vs -11.5 ± 5.5 kg, $p \geq 0.50$) • Lower BP (-9.8 ± 11.6 mmHg vs -7.3 ± 6.8 mmHg, $p \geq 0.10$)LC vs HC in patients with A1c > 7.8%: • Improved A1c ($-2.6 \pm 1.0\%$ vs $-1.9 \pm 1.2\%$, $p = 0.002$) • Reduced TG (-0.5 ± 0.5 mmol/L vs -0.1 ± 0.5 mmol/L, $p \leq 0.03$)Increased HDL (0.2 ± 0.3 mmol/L vs 0.05 mmol/L, $p = 0.007$)
Brinkworth (2016)[51] – extension of Tay (2014)				Weight Mood (POMS, BDI, SAI) Diabetes emotional distress (PAID) QoL (D-39)		LC and HC: • 9.5 ± 0.5 kg weight loss (9%, $p = 0.91$) • Improved POMS, BDI, PAID, and D-39 (most dimensions)

Urbanova (2017)[72]	N = 11 obese patients N = 16 type 2 DM obese patients *N* = 17 healthy non-obese controls	3 weeks	Very low carbohydrate diet (VLCD)	Body composition Glucose metabolism Cholesterol	Compliant	VLCD in obese DM patients reduced: • Weight vs. control ($p < 0.05$) and from baseline (141.6 ± 5.9 kg to 129.9 ± 5.3 kg, $p < 0.001$) • BMI vs. control ($p < 0.05$) and from baseline (51.5 ± 2.0 kg/m^2 to 47.3 ± 1.9 kg/m^2, $p < 0.001$) • Waist circumference (140 ± 4 cm to 135 ± 4 cm, $p < 0.001$) • Fasting insulin ($p < 0.001$) • TC (4.67 ± 0.20 mmol/L to 3.98 ± 0.20 mmol/L, $p = 0.006$) • LDL (2.84 ± 0.18 mmol/L to 2.19 ± 0.20 mmol/L, $p = 0.037$) • TG (1.81 ± 0.15 mmol/L to 1.55 ± 0.14 mmol/L, $p < 0.0001$) VLCD in obese DM patients increased HDL (1.02 ± 0.04 mmol/L to 1.09 ± 0.19 mmol/L)

BP = Blood pressure, A1c = Hemoglobin A1c, TG = Triglycerides, QoL = Quality of life, POMS = Profile of Mood States, BDI = Beck Depression Inventory, SAI = Spielberger State Anxiety Inventory, PAID = Problem Areas in Diabetes Questionnaire, D-39 = QoL Diabetes-39, PCOS = Polycystic ovary syndrome, AA = African American, DM = diabetes, TC = total cholesterol.

Sheets based on the study protocol were used to increase consistency in reporting. Search strategies and results along with article PDFs were saved in the folder along with a copy of the article and citation in the RefWorks® (ProQuest LLC) system.

2.7. Economic impact

Since cost was not directly evaluated in these studies, and in order to contextualize the economic impact of the key clinical outcomes identified, each of the key findings from the systematic review were aggregated into ranges describing the amount of change noted across relevant studies. Then, the peer-reviewed literature and national websites with cost information were searched to identify costs associated with each positive or negative clinical outcome. These searches were performed using information available in 2019. For example, the costs of a hospitalization related to myocardial infarctions was determined and then applied when hospitalizations were reduced.

3. Results

A total of 1968 studies were identified through the literature search and hand searching process, and after applying inclusion and exclusion criteria, 57 studies (27,449 patients) remained (see Fig. 1).

3.1. Systematic review

In diabetes, articles were identified when they included low-carbohydrate or low-calorie diets, and a total of 8 articles ($n = 459$ patients) were included (see Table 2). Implementation of these diets resulted in weight, BMI, waist circumference, or fat reduction (8 studies); improved/reduced A1c or fasting insulin (6 studies); and improvement in cholesterol (3 studies).

In heart disease, articles were identified when they included the DASH diet or the Mediterranean diet, and a total of 10 DASH diet ($n = 11,891$) and 14 Mediterranean diet ($n = 18,500$) articles were included (see Tables 3 and 4, respectively). Implementation of a DASH diet resulted in improved blood pressure control, lowered blood pressure, or reduced mean arterial pressure (7 studies); weight, BMI, waist circumference, or fat reduction (3 studies); and metabolic syndrome criteria improvement (3 studies). Implementation of a Mediterranean diet resulted in improvement in cholesterol (9 studies); reduced cardiovascular risk or improved CV risk markers (6 studies); and improved blood pressure control, lowered blood pressure, or reduced mean arterial pressure (5 studies).

In geriatrics, articles were identified when they included dietary interventions for geriatric patients, and a total of 7 articles ($n = 714$) were included (see Table 5). Implementation of a broad range of diets that included more fresh fruits and vegetables, increased protein, and higher energy intake, often in collaboration with resistance training or other exercise, resulted in improved weight, fat-free mass, or muscle mass (3 studies). Other results related to geriatrics were varied among studies.

In chronic kidney disease, articles were identified when they included dietary interventions for chronic kidney disease patients, and a total of 7 articles ($n = 637$) were included (see Table 6). Commonly utilized diets within these studies were fixed protein, oral NaHCO3, and daily addition of flaxseed oil. Implementation of protein-controlled or nutrient-specific controlled diets resulted in: improved GFR or dialysis-free time (2 studies). Other factors considered in these studies were inflammation markers, urine phosphorus, SBP, and CrCL; however these were not consistent across all articles.

In neurology/cognition, articles were identified when they included dietary interventions for neurologic issues, which included cognition and depression, and a total of 10 articles ($n = 5182$) were included (see Table 7). Implementation of nutrient-specific diets (often antioxidant or flavonoid-related) resulted in improved cognition (7 articles). Other results varied among studies with benchmarks such as constructional praxis, long-term

Table 3
Article summaries of the DASH diet in heart disease.

Author (Year)	N	Study Length	Diet Assignments	Outcomes Assessed	Adherence/Compliance	Key Findings
Haring (2014)[46]	N = 155, Caucasian and African American patients	3-period crossover of 6 weeks each	DASH-type diet + increased carbohydrates DASH-type diet + increased protein DASH-type diet + increased unsaturated fat	Lipoprotein A [Lp (a)] – independent risk factor for CVD	100% - noncompliant excluded	DASH + unsaturated fat resulted in: • Increased mean Lp(a) levels less than the DASH + carbohydrate diet (21.1 mg/dL; 95% CI: 20.1 to 22.1, p = 0.026)DASH + protein resulted in increased Lp(a) concentration more than the: • DASH + carbohydrate diet (1.4 mg/dL; 95% CI: 0.4 to 2.4, p = 0.005) • DASH + unsaturated fat (2.5 mg/dL; 95% CI, 1.5 to 3.5, p = 0.001)
Hikmat (2014)[38] DASH Trial	N = 311 non-metabolic syndrome patients N = 99 metabolic syndrome patients	8 weeks	Fruits and vegetables diet DASH diet Control	Change in BP HTN Control	DASH = 93.2% Fruit/Vegetable = 93.9% Control = 94.6%	Metabolic syndrome patients - DASH diet resulted in: • Reduced SBP vs control (4.9 mmHg, p = 0.006) • Reduced DBP vs control (1.9 mmHg, p = 0.15) • Greater unadjusted BP control (67% vs 17%, $p < 0.05$) • Greater adjusted BP control (75%, OR = 9.5, $p < 0.05$) Non-metabolic syndrome patients - DASH diet resulted in: • Reduced SBP vs control (5.2 mmHg, $p < 0.001$) • Reduced DBP vs control (2.9 mmHg, p < 0.001) • Greater BP control (57% vs 15%, OR = 7.7, p = 0.001)
Hill (2015)[58] BOLD Study	N = 62 overweight adults with metabolic syndrome	6 months	Modified DASH diet rich in plant protein Modified DASH diet rich in animal protein (BOLD) Moderate protein diet (BOLD+) Included a meals provided phase, meals + exercise (weight-loss) and a "free-living" phase (participants made changes on their own)	Change in metabolic syndrome criteria	M-DASH = 84% ± 1% BOLD = 81% ± 3% BOLD+ = 74% ± 2%	Adherence to any one of the three diets resulted in: • ≥5% weight loss • Decrease in metabolic syndrome criteria: waist circumference, HDL, TG, glucose, SBP, DBP ($p < 0.05$) Every 1% reduction in body weight was associated with a: • 39% increase in the odds of having a resolution of metabolic syndrome during the weight loss phase • 88% increase in the odds of having a resolution of metabolic syndrome during the normal life phase
Roussel (2014)[39] Secondary analysis of the BOLD Study	N = 36 normotensive patients	5 weeks	Healthy American diet (control)	Weight BP Endothelial function	93%	Adherence to the BOLD diet resulted in: • Decreased SBP vs control (p < 0.05). Average reduction = 4.2 mmHg No other significnat findings.
Hummel (2013)[59]	N = 13 heart failure with preserved ejection fraction (HFPEF) patients	21 days	DASH + sodium-restricted diet (SRD)	BP measurement 6-min walking test 24-h urinary collection ECHO (assessed heart function, energy, stiffness, thickness)	"Excellent"	Adherence to the DASH + SRD diet resulted in: • Reduced clinic and 24-h brachial systolic pressure (155 ± 35 to 138 ± 30 and 130 ± 16 to 123 ± 18 mmHg; both p = 0.02) • Improved diastolic function (p = 0.03)
Jenkins (2017)[45]	N = 209 men N = 710 women who were healthy & overweight	18 months	DASH diet advice DASH weekly food provision (food basket) DASH diet advice + weekly food provision Control (Health Canada's food guide)	Bloop panels Anthropometric measurements BP	Highest retention with food provision vs not provided (91% vs 67% at 6 months 81% vs 57% at 18 months, p < 0.001)	Adherence to advice or diets resulted in significantly improved at 6 months: • Body weight (−0.8 to −1.2 kg loss) • Waist circumference (−1.1 to 1.9 cm loss) • Mean arterial pressure (0.0 to −1.1 mmHg reduction) Adherence to advice or diets resultsed in significantly improved Framingham score (−0.19 to −0.42%) at 18 months.
Johansson-Persson (2014)[73]	N = 24 overeight patients with high cholesterol	5 weeks	High fiber (48 g) Low fiber (30.2 g)	LDL Glucose Lipid metabolism Inflammatory markers	High dietary fiber diet had significantly higher compliance (60.7% vs. 34.4%, p = 0.027)	Adherence to the high fiber diet resulted in: • Reduced C-reactive protein (p = 0.017) • Reduced fibrinogen (p = 0.044) No other significant effects

Juraschek (2017)[60] DASH Trial	N = 412 (57% women, 57% African American)	4 weeks (each sodium level for 30 days)	DASH groups of low (50 mmol/day), medium (100 mmol/day), and high (150 mmol/day) sodium intake Control groups of: low (50 mmol/day), medium (100 mmol/day), and high (150 mmol/day) sodium intake	SBP DBP	High diet adherence	Reducing sodium from high to low in control group was associated with lower SBP from baseline (p for trend = 0.004): • Baseline SBP <130: −3.20 (−4.96, −1.44), p < 0.001 from baseline • Baseline SBP 130–139: −8.56 (−10.70, −6.42), p < 0.001 from baseline and vs. SBP < 130 baseline • Baseline SBP 140–149: −8.99 (−11.21, −6.77), p < 0.001 from baseline and vs. SBP < 130 baseline • Baseline SBP ≥150: −7.04 (−12.92, −1.15), p = 0.02 from baseline and p = 0.20 vs. SBP < 130 baseline Reducing sodium from high to low in the DASH group was associated with lower SBP from baseline (p for trend<0.001): • Baseline SBP <130: −0.88 (−2.07, 0.30), p = 0.14 from baseline • Baseline SBP 130–139: −3.29 (−4.71, −1.88), p < 0.001 from baseline and p = 0.01 vs. SBP < 130 baseline • Baseline SBP 140–149: −4.90 (−7.25, −2.55), p < 0.001 from baseline and p = 0.003 vs. SBP < 130 baseline • Baseline SBP ≥150: −10.41 (−15.54, −5.28), p < 0.001 from baseline and vs. SBP < 130 baseline The greatest impact of DASH + low sodium diet was seen in the high SBP group.
Kirwan (2016)[44]	N = 40 overweight/ obese patients	8 weeks each (crossover)	Complete whole grain Refined grain (control)	BP Body composition Lipids Glucose Inflammatory markers	Adherence in both groups was similar: • Whole grain: 94.6% ± 6.4% • Refined grain: 92.9% ± 5.7%	Adherence to the whole grain diet resulted in: • Lower DBP overall and vs. control (−5.8 mmHg, 95% CI: −7.7, −4.0 mmHg vs −1.6 mmHg, 95% CI: −4.4, 1.3 mmHg, p = 0.01) • Lower Mean Arterial Pressure (−5.0, 95% CI: −7.2, −2.9, p < 0.001) • Reduced metabolic syndrome severity (p = 0.04) • Lower HbA1c (−0.13, 95% CI: −0.01, −0.25, p = 0.04) Both diets resulted in significantly reduced: • Weight • BMI • Fat mass • Body fat % • Fat free mass • Waist circumference • TC
Sayer (2015)[40]	N = 19 with elevated BP	6 weeks each (crossover)	DASH + pork DASH + chicken and fish	SBP DBP	≥95% for both interventions	Adherence to either DASH diet resulted in: • Reduced SBP and DBP by 7 mmHg and 6mmgHg seated and 24-h by 7 mmHg and 4 mmHg (p < 0.05) No significant difference between groups

BP = Blood pressure, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, A1c = Hemoglobin A1c, TG = Triglycerides, DM = diabetes, TC = total cholesterol, MD = Mediterranean Diet, HDL = high density lipoprotein.

Table 4
Article summaries of the Mediterranean diet in heart disease.

Author (Year)	N	Study Length	Diet Assignments	Outcomes Assessed	Adherence/Compliance	Key Findings
Casas (2014)[36] PREDIMED Study	*N* = 164	1 year	MD w/EVOO MD w/nuts Low-fat diet MD Low-fat foods	BP Lipids Markers of inflammation	Higher in the MD arms	Adherence to a MD resulted in: • Lower SBP and DBP (-6 mmHg, -3 mmHg, p = 0.02) • Reduced LDL by 10% MD + EVOO and by 8% MD + nuts (p = 0.04) • Reduced waist circumference (p < 0.05) • Reduced inflammatory markers (p < 0.05) vs control
Casas (2016)[37] PREDIMED Study	*N* = 165	5 years				Adherence to a MD resulted in: Reduced inflammatory markers (p = 0.04) Lower SBP (p ≤ 0.05) • MD + EVOO = −6.2 mmHg at 3 years, −9.7 mmHg at 5 years • MD + nuts = −7.2 mmHg at 3 years, −10.9 mmHg at 5 years Lower DBP (p ≤ 0.05) • MD + EVOO = −5.3 mmHg at 3 years, −7.2 mmHg at 5 years • MD + nuts = −5.5 mmHg at 3 years, −7.8 mmHg at 5 years Lower LDL (p ≤ 0.05) • MD + EVOO = −11.7 mg/dL at 3 years, −23.8 mg/dL at 5 years • MD + nuts = −16.5 mg/dL at 3 years, −44.2 mg/dL at 5 years Lower TC (p ≤ 0.05): • MD + EVOO = −19.2 mg/dL at 3 years, −31.1 mg/dL at 5 years • MD + nuts = −18.4 mg/dL at 3 years, −39.1 mg/dL at 5 years Increased HDL (p ≤ 0.05): • MD + EVOO = 7.5 mg/dL at 3 years, 4.4 mg/dL at 5 years • MD + nuts = 6.5 mg/dL at 3 years, 7.4 mg/dL at 5 years Improved Body Composition (p ≤ 0.05) • MD + EVOO at 3 years = −0.8 kg weight, −0.3 kg/m^2 BMI, −4.0 cm waist circumference • MD + EVOO at 5 years = −1.3 kg weight, −0.5 kg/m^2 BMI, −1.2 cm waist circumference • MD + nuts = −2.8 cm at 3 years and − 1.6 cm at 5 years waist circumference
Medina-Remón (2017)[41] PREDIMED Study	*N* = 1139 high-risk	1 year				Adherence to a MD resulted in lower SBP and DBP and greater HDL (*p* < 0.05): • −3.8 mmHg to −4.6 mmHg reduction in SBP • −1.8mmgHg to −1.9 mmHg reduction in DBP • 2.6mmgHg to 5.6 mmHg increase in HDL
Estruch (2013)[74] PREDIMED Study *Retracted and Republished*[a]: Estruch (2018)[62]	*N* = 7447, 1588 participants were eliminated that deviated from protocol	4.8 years		CV event rates (MI, stroke, death)		Adherence to a MD resulted in: • Lower risk of CV events vs control: ○ Unadjusted: MD + EVOO HR = 0.69, 95% CI: 0.53–0.91; MD + nuts HR = 0.72, 95% CI: 0.54–0.95 ○ Adjusted for adherence: HR = 0.42 (95% CI, 0.25–0.63) • Significant reduction in CV events vs control (MD + EVOO 96 events, 3.8%; MD + nuts 83 events, 3.4%; control 109 events, 4.4%) • Significant reduction in stroke vs control (MD + EVOO 39 events, *p* = 0.03; MD + nuts 32 events, *p* = 0.003; control 58 events) • Adherence-adjusted HR for lower risk of CV event No other significant differences
Castaner (2013)[47] PREDIMED	*N* = 34 patients with CVD risk factors	3 months		Lipids (TC, HDL, TG) Gene transcription		Adherence to a MD resulted in: • Impact on gene transcription which could result in CV event prevention No significant difference in lipids.

Table 4 (*continued*)

Author (Year)	N	Study Length	Diet Assignments	Outcomes Assessed	Adherence/Compliance	Key Findings
Study						
Fito (2014)[48] PREDIMED Study	*N* = 930 patients at high CV risk	1 year		HF Biomarkers: NT-pro BNP, OxLDL, Lp(A)		Adherence to a MD resulted in: • Decreases in NT-pro BNP overall and vs control ($p < 0.05$) • OxLDL decreased significantly overall ($p < 0.05$) • Less changes in Lp(A) ($p = 0.046$) Adherence to the MD + EVOO resulted in: • OxLDL decreased significantly vs control ($p = 0.003$)
Toledo (2013)[42] PREDIMED Study	N = 7447	4 years		BP		Adherence to a MD resulted in: • Lower BP than control (MD + EVOO: −1.53 mmHg, 95% CI: −2.01, −1.04 mmHg; MD + nuts: −0.65 mmHg, 95% CI: −1.15, −0.15 mmHg) Dietary adherence overall resulted in a greater percentage of patients with controlled BP ($p < 0.001$): • MD + EVOO: 33.6% (95% CI: 31.7, 35.5%) at baseline to 39.9% (95% CI: 37.4, 42.3%) at year 4 • MD + nuts: 31.1% (95% CI: 29.3, 33.0) at baseline to 41.5% (95% CI: 38.8, 44.3%) at year 4 • Control: 31.1% (95% CI: 29.2, 33%) at baseline to 42.6% (95% CI: 39.5, 35.7%) at year 4
Davis and Hodgson (2017)[43] MedLey study	*N* = 166 older adults	6 months	MD Habitual diet (control)	BP Flow-mediated dilation (FMD)	MD significant improvement in adherence from med to high vs. control ($p < 0.001$)	Adherence to a MD resulted in (vs control): • Lower SBP at 3 months (−1.3 mmHg, $p = 0.008$) and 6 months (−1.1 mmHg, $p = 0.03$) • FMD % higher at 6 months ($p = 0.026$)
Davis and Bryan (2017)[49] MedLey study				Lipids (TG) F2-isoprostanes	"Good"	Adherence to a MD resulted in (vs control): • Lower TG at 3 months (−0.15 mmol/L, $p < 0.001$) and 6 months (−0.09 mmol/L, $p = 0.03$) • Lower F2-isprostanes at 6 months ($p < 0.001$)
De Lorenzo (2017)[75]	*N* = 25 patients with metabolic syndrome	1 day	MD Western, high fat diet (control)	Ox-LDL	100%	Adherence to a MD resulted in: • Lower Ox-LDL levels vs. control ($p < 0.05$)
Gomez-Delgado (2015)[76]	*N* = 897 patients with the "CLOCK" gene and CHD	1 year	MD Low-fat foods (control)	C-reactive protein levels (CRP) HDL levels	Not listed	Adherence to a MD resulted in: • Decrease in CRP ($p < 0.001$) • Increase in HDL ($p = 0.029$)
Ruscica (2016)[61]	N = 26 with MetS	12 weeks	MD + soy protein MD + animal protein	Metabolic syndrome features Biomarkers associated with CV risk	>95% to both diets	Adherence to a MD + soy protein resulted in ($p < 0.05$): • Reduced median TC (−4.8%) • Reduced median LDL-C (−5.2%) • Reduced non-HDL-C (−7.1%) • Reduced apoB (−14.8%)
Richard (2013)[63] Richard (2014)[77]	*N* = 26 males with MetS (19 males for last phase)	35 weeks	5 weeks normal American diet – isocaloric (control) 5 weeks MD – isocaloric 20 weeks free-living (no food provided) For those that lost ≥5% of body weight: 5 weeks MD - isocaloric	Body composition Biomarkers associated with CV risk Apolipoprotein B100 (apoB100) metabolism	Only adherent to the MD when food was provided	Adherence to a MD resulted in ($p < 0.05$) vs control period: • Reduced CRP concentrations (−26.1%) • Greater weight loss (−10.2 ± 2.9%) • Reduced waist circumference (−8.6 ± 3.3 cm) Adherence to a MD resulted in: • Reduced LDL-apoB100 concentration ($p < 0.01$)

BP = Blood pressure, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, A1c = Hemoglobin A1c, TG = Triglycerides, DM = diabetes, TC = total cholesterol, MD = Mediterranean Diet, HDL = high density lipoprotein, EVOO = extra virgin olive oil, CV = cardiovascular, CVD = cardiovascular disease.

[a] Due to retraction, the 2013 article was eliminated and replaced with the republished version in June 2018.

Table 5
Geriatrics article summaries.

Author (Year)	N	Study Length	Diet Assignments	Outcomes Assessed	Adherence/Compliance	Key Findings
Anbar (2014)[78]	$N = 50$ geriatric patients	≥14 days	Caloric restriction with oral nutritional supplements (based on energy goal) Control	Resting energy expenditures Length of hospital stay Complication incidence	Compliant	Caloric restriction resulted in: • Fewer complications, mainly due to lower infection rates (surgical, infectious, cardiovascular, gastrointestinal, delirium, deep vein thrombosis, development of new pressure sores) (27.3% vs. 64.3%, $p = 0.012$) • Shorter length of hospitalization (10.1 ± 3.2 days vs 12.5 ± 5.5 days, $p = 0.061$) Calorie intake correlated to: • Lower complication rate ($r = -0.417$, p = 0.003) • Shorter length of stay ($r = -0.282$, $p = 0.049$)
Aparicio (2013)[81]	$N = 140$ institutionalized elderly from Madrid, Spain	7 days	Glycemic Index (GI) and glycemic load (GL) via food provided by nursing home	Depression (GDS) – separated into non-depressed and depressed	Compliant	Patients with a higher GL were: • Less likely to be depressed ($p < 0.01$) There were no differences in GI between depressed and non-depressed.
Collins (2017)[80]	$N = 122$ subacute ward patients	14 days	High energy and protein diet Control	Weight Hand grip strength Patient satisfaction Cost	Compliant	No significant differences between groups in outcomes. Intervention group had: • More intake of energy (p = 0.003) • Greater protein intake ($p = 0.035$)Higher costs (4.15 pounds (£)/patient/day)
Daly (2014)[84]	$N = 100$ elderly women	4 months	Progressive resistance training + lean red meat (160 g 6 days/week) Control: progressive resistance training +1 serving pasta or rice/day	Muscle mass and composition Inflammatory markers Blood pressure Lipids	81% meat compliance 100% carbohydrate compliance 92% VitD supplement compliance	Allocation to the lean red meat group resulted in: • Greater increase in insulin like growth factor 1 ($p < 0.05$) • Decrease in inflammatory markers like IL-6 (p < 0.05) • Greater gains in today body and leg lean tissue mass as well as muscle strength (p < 0.05)No difference was seen in BP or lipid panel.
Denissen (2017)[82]	$N = 40$ functionally disabled home-dwelling elderly	12 weeks	Home meal delivery service of a high quality dinner with fresh ingredients using the Netherlands Nutrition Centre Foundation guidelines (which includes low sodium) Control	Satisfaction with service Body composition QoL	Compliant	Intervention group: • >90% were satisfied with taste and quality • 70% would want a similar service in the future • Increase in weight (p < 0.05) • Increase in BMI ($p < 0.005$) • Increase in upper leg circumference (p < 0.01) • Increase in fat free mass ($p < 0.03$) • No difference in QoL
Kitzman (2016)[79]	N = 100 older obese men and women	20 weeks	Exercise alone Diet alone (caloric restriction, ~400 kcal/day deficit) Diet (~350 kcal/day deficit) Control	Exercise capacity QoL (MLHF)	Dietary compliance was 99 ± 1% for both diet groups.	All intervention groups had significant improvements in exercise capacity ($p < 0.001$). No change in quality of life
Reidlinger (2015)[83]	$N = 162$ nonsmoking men and women	12 weeks	United Kingdom dietary guidelines (low sodium, low fat, low sugar while increasing fish, fruits, vegetables, and whole grains) Control (traditional British diet)	SBP TC HDL Weight	Compliant	Adherence to dietary guidelines resulted in: • Lower SBP (4.2 mmHg, p < 0.001) • Lower body weight (1.9 kg, $p < -0.001$) • Improved TC:HDL ratio (0.13, $p = 0.044$) Diets were "well accepted and did not differ in cost."

QoL = Quality of life, MLHF = Minnesota Living with Heart Failure Questionnaire, GDS = Geriatric Depression Scale, SBP = Systolic blood pressure, TC = Total cholesterol.

memory, memory discrimination, and depression, but these were not consistent across all articles.

All included articles had Level A or B methodological quality, indicating that the bias did not invalidate the results. There was a broad range of applicability of the studies, and no studies had a harmful effect. Table 8 breaks down articles by their overall effect in column 4, where there were mostly studies that were clinically meaningful but not conclusive (58.9%, $n = 33$), and second most clinical meaningful benefit fully demonstrated (33.9%, $n = 19$).

3.2. Economic impact

After the systematic review was completed, a compilation of changes in clinical outcomes was compiled with ranges of impact (see Table 9). Key

Table 6
Chronic kidney disease / kidney article summaries.

Author (Year)	N	Study Length	Diet Assignments	Outcomes Assessed	Adherence/Compliance	Key Findings
Friedman (2014)[55]	$N = 8$ severely obese patients with normal kidney function	7 days	Fixed protein (50 g/day)	Glomerular filtration rate (GFR)	100% compliance	GFR was statistically lower after surgery ($p < 0.01$). Low protein diet did not alter GFR ($p = 0.07$)
Goraya (2013)[85]	$N = 71$ Stage 4 CKD patients	1 year	Oral $NaHCO_3$ daily Base-producing fruits and vegetables	eGFR $PTCO_2$ Kidney injury Weight SBP	Not listed	Adherence to base-producing fruits and vegetables resulted in: • Reduction in weight: 82.7 ± 6.1 kg to 78.0 ± 5.3 kg (p < 0.01) • Reduction in SBP: 136.1 ± 4.7 to 131.7 ± 3.3 (p < 0.01) • Stable eGFR • Increased $PTCO_2$ (p < 0.01)Lower urine indices of kidney injury
Moorthi (2014)[54]	$N = 13$ patients with CKD	4 weeks	70% plant protein omnivorous diet	Changes in 24 h urine phosphorus	Median = 95% compliance (94% in first two weeks, 97% in last two weeks)	Urine phosphorus significantly decreased by 215 ± 232 mg/day ($p < 0.001$)
Piccoli (2016)[53]	$N = 449$ CKD patients	847 patient-years of observation	Moderately-restricted low protein diet (0.6 g/kg/day of protein)	Dialysis-free time Mortality rates Cost savings	Compliant	Dialysis-free time for patients with low GFR (≤15 mL/min): • 50% dialysis-free for 2 years • 25% dialysis free for 5 years Lower mortality rates than for patients on dialysis: • United States Renal Data System (USRDS): 0.44 (0.36–0.54) • Italian Dialysis Registry: 0.73 (0.59–0.88) • French Dialysis Registry 0.70 (0.57–0.85) Calculated cost savings: • 1–4 million Euros for every 100 patients80.6–94.3% per 100 patients
Tabibi (2017)[56]	$N = 38$ hemodialysis patients	8 weeks	Flaxseed oil (6 g/day) Control	Hematologic factors Serum hepcidin concentration	90% compliance	Adherence to flaxseed oil resulted in: • Reduction in serum hepcidin concentration (25%, p < 0.01)Increase in hematologic factors (p < 0.01)
Mirfatahi (2016)[86]	$N = 34$ hemodialysis patients			Inflammation markers Oxidative stress		Adherence to flaxseed oil: • Significantly reduced several inflammation markers that are risk factors for CVD ($p < 0.05$)
Wada (2015)[57]	$N = 24$ patients with IgA nephropathy	4–5 days	Hospital diet: 120 mEq sodium, 65 g protein, 1800 kcal of energy Control: home diet	Differences in creatinine clearance (CrCl) and glomerular filtration rate (GFR)	100% compliance	Changes in dietary protein intake were correlated with changes in glomerular filtration rate ($r = 0.726$, p < 0.001) and associated with CrCl

$PTCO_2$ = Plasma total CO_2.

findings from the systematic review indicated that providing food to patients resulted in high rates of dietary adherence in heart disease (HTN, HF), diabetes, and CKD. With dietary guidelines adherence, it was observed that HTN was improved through SBP reduction, DBP reduction, and greater control achievement. CV events also were reduced, and patients had improvements in lipids, A1c, and weight loss. Many patients also had resolution of or reduction of the metabolic syndrome criteria.

These findings were then examined in context of the literature. Each of these findings had substantial implications for patient disease progression, morbidity, and mortality as well as healthcare system resource utilization and costs. Literature review showed these outcomes would result in: lower CV event risk (20–30% reduction: $5–11 billion annually), decreased hospitalization costs ($1–8 billion), and lower dialysis rates (25–50% reduction: $14–29 billion annually). For heart failure patients, results include: 16% fewer readmissions and a 38-day shorter length of stay, resulting in a savings of $234,096 per 100 patients (decreased readmissions) and $79,425 per hospitalization. For diabetes, patients were compliant and reduced their A1c (0.9–2.6%). Reducing A1c by 1.5% could result in $11.6–20 billion in savings to the US healthcare system. Further, these reductions often brought A1c levels under 9%, which would result in $1.8 billion in annual savings. In CKD, 25–50% of ESRD patients became dialysis-free, which could lead to $14.7–29.4 billion in annual savings.

4. Discussion

The studies presented within this review indicate that provision of medically-tailored meals may indeed provide a novel strategy to helping patients meet their nutrition goals and thereby improving numerous health outcomes. Patient adherence was high when food or meal items were provided, and patients often experienced reduction in key clinical outcomes, such as decreased weight and BMI, improved A1c, lowered blood pressure,

Table 7
Cognition article summaries.

Author (Year)	N	Study Length	Diet Assignments	Outcomes Assessed	Adherence/Compliance	Key Findings
Boespflug (2018)[96]	$N = 21$ adults ages 68 or older with age-related memory decline	16 weeks	Freeze-dried whole fruit blueberry powder (flavonoids) Placebo powder	Functional magnetic resonance imaging during a working memory task to examine blood oxygen level-dependent (BOLD) signaling	Assessed but actual rates not provided	Adherence to blueberries resulted in: • Increased BOLD activation ($p < 0.01$) There was no impact on working memory enhancement.
Cardoso (2014)[91]	N = 20 older adults with mild cognitive impairment	6 months	Brazil nuts (selenium) – one Brazil nut daily Control	Blood selenium concentrations Antioxidant enzymes (erythrocyte glutathione peroxidase (GPx) activity, oxygen radical absorbance capacity, and malondialdehyde) Change in cognition: CERAD neuropsychological battery (animal naming, Boston naming, word list learning, constructional praxis, word list recall, recognition)	All but 3 patients had ≥85% compliance.	Adherence to the brazil nut diet resulted in: • Increased blood serum selenium concentrations ($p < 0.001$) vs control • Increased GPx activity vs control ($p = 0.006$) • Increased verbal fluency ($p = 0.007$) Increased constructional praxis ($p = 0.031$)
Kent (2017)[87]	$N = 49$ adults ≥70 years with mild-to-moderate dementia	12 weeks	Cherry Juice 200 mL/day (flavonoid-rich food = anthocyanis) Control (apple juice)	BP Inflammatory markers (CRP and IL-6) Change in cognition: • RAVLT • SOPT • Boston naming test • TMT • Digit span backwards taskCategory/letter verbal fluency)	Unknown	Adherence to the cherry juice resulted in: • Improvement in verbal fluency ($p = 0.014$) • Improvement in long-term memory ($p < 0.001$) • Reduced SBP (138.2 ± 16.4 to 130.5 ± 12.2, $p = 0.038$)) Inflammatory markers were not changed.
McNamara (2018)[95]	$N = 94$ adults ages 62–80 years with mild cognitive decline	24 weeks	Daily fish oil Daily blueberry (flavonoids) Fish oil + blueberry	Change in cognition: • DEX • TMT-A • TMT-B • Controlled Oral Word Production • Hopkins Verbal Learning Test	Assessed but actual rates not provided	Combined had no cognitive improvement. Adherence to fish oil resulted in: • Fewer cognitive symptoms ($p = 0.03$) Adherence to blueberries resulted in: • Fewer cognitive symptoms but not significantImproved memory discrimination ($p = 0.04$)
Ota (2016)[88]	N = 19 adults ≥60 years with no dementia	1 meal	Ketogenic meal (20 g of medium chain TGs) Control (isocaloric meal)	Global cognitive score from 3 tests: • TMT-A and TMT-B • Digit SpanVisual Memory Span	Compliant	Adherence to the ketogenic meal resulted in: • Improved global score overall ($p = 0.017$) Improved global score for patients with a low baseline score ($p = 0.005$)
Scott (2017)[90]	$N = 48$	6 months	Avocado (Lutein): 135 g/day (approximately 1.33 avocado per day) Control (Potato/chickpeas)	Serum lutein Macular pigment density Change in cognition: • CRT • RVIP • DMS • PAL • SSP & SSP-R • SWM • SOC	98% compliance	Adherence to the avocado diet resulted in: • Increased serum lutein levels ($p = 0.001$) • Improved macular pigment density ($p = 0.001$) • Improved sustained attention ($p = 0.033$) • Improved cognition from baseline.
von Arnim (2013)[89]	$N = 39$ adults 61–87 years with mild/moderate cognitive impairment	2 months	Micronutrient Supplement (antioxidant, zinc, B vitamin)	Blood levels of vitamins Nutritional status (Mini Nutritional Assessment)	99% compliance	Adherence to the vitamins resulted in: • Significant improvement in blood levels of B vitamins ($p < 0.05$), folic acid ($p < 0.001$), lutein ($p < 0.01$), a-carotene ($p < 0.05$) • Improved MNA score for those at risk for malnutrition ($p < 0.05$)
Martinez-Lapisncina (2013)[92] PREDIMED Study	$N = 522$ adults at high vascular risk	6.5 years	Mediterranean diet with EVOO Mediterranean diet with nuts Control (low-fat diet) Mediterranean diet with EVOO	Global cognitive performance: • MMSE • CDT	Good Good, with Mediterranean diet groups having greater adherence	Adherence to the Mediterranean diet + EVOO resulted in: • Higher mean MMSE scores vs control (adjusted differences: +0.62, 95% CI +0.18 to +1.05, $p = 0.005$) • Higher mean CDT scores vs control (adjusted differences: +0.51 95% CI +0.20 to +0.82, $p = 0.001$) Adherence to the Mediterranean diet + nuts resulted in:

Table 7 (*continued*)

Author (Year)	N	Study Length	Diet Assignments	Outcomes Assessed	Adherence/Compliance	Key Findings
			Mediterranean diet with nuts Control (low-fat diet)			• Higher mean MMSE scores vs control (adjusted differences: +0.57, 95% CI +0.11 to +1.03, $p = 0.015$)Higher mean CDT scores vs control (adjusted differences: +0.33 95% CI +0.003 to +0.67, $p = 0.048$
Valls-Pedret (2015)[93] PREDIMED Study	$N = 447$ cognitively healthy older adults	Median = 4.1 years		Change in cognition: • MMSE • RAVLT • Wechsler Memory Scale • Animal fluency test • Digit Span subtest (Wechsler Adult Intelligence Scale) • Color Trail Test • [Created composite score]		Control group: • Composite cognitive decline from baseline (−0.17; 95% CI: −0.32 to −0.01, p < 0.05) Adherence to the Mediterranean diet + EVOO resulted in: • Higher scores on the RAVLT vs control ($p = 0.049$) • Higher scores on the Color Trail Test Part 2 vs control (p = 0.04) • Less composite cognitive decline vs control (0.04; 95% CI: −0.09 to 0.18, p = 0.04) Adherence to the Mediterranean diet + nuts resulted in: • Less composite cognitive decline vs control (0.09; 95% CI: −0.05 to 0.23, p = 0.04)
Sáchez-Villegas (2013)[94] PREDIMED Study	$N = 3923$ adults	Median = 5.4 years		• Incidence of depression		224 new cases of depression Adherence to a MD resulted in no significant association with the risk of developing depression. Adherence to a MD in patients with type 2 diabetes resulted in a significant inverse association with the risk of developing depression (HR = 0.59, 95% CI: 0.36–0.98).

BP = Blood pressure, TG = triglyceride, RAVLT = Rey Auditory Verbal Learning Test, SOPT = self-ordered pointing task, TMT = trail making test, CRT = Choice Reaction Time, RVIP = Rapid Visual Information Processing, DMS = Delayed Match to Sample, PAL = Paired Associates Learning, SSP = Spatial Span, SSP-R = Spatial Span Reverse, SWM = Spatial Working Memory, SOC = Stocking of Cambridge, CERAD = Consortium to Establish a Registry for Alzheimer's Disease, EVOO = Extra Virgin Olive Oil, MMSE = Mini Mental Status Exam, CDT = Clock Drawing Test, DEX = Dysexecutive Questionnaire.

and improved renal function. Dietary modification is a key component of medical therapy in the treatment of many chronic diseases, including diabetes, cardiovascular disease, and chronic kidney disease. Treatment guidelines for these prominent chronic diseases prioritize dietary changes including reduced salt intake, increase fruit and vegetable consumption, and reduced consumption of processed carbohydrates and saturated fats.[25–28] However, the required dietary changes are often complex and inconvenient, especially when multiple comorbidities are present. Additionally, patients are often not equipped with the required knowledge, skills, time, and resources to adequately plan, cook and eat meals that adhere to the recommended diet. Patients in one study with end stage renal disease found that patients' knowledge of their dietary recommendations was often limited, and most patients followed the dietary patterns of their surrounding family members, rather than following guideline-based dietary advice.[29] Similar studies have indicated that many patients with diabetes or cardiovascular disease also have limited knowledge of the impact of diet on their conditions.[30–32]

As patients experience many barriers to dietary adherence, including limitations in knowledge, health beliefs, and required resources, adherence to dietary recommendations remains low. In a study evaluating the dietary patterns of patients with diabetes, only 22% of sampled patients with type 1 and type 2 diabetes reported adhering to dietary recommendations.[33] Other studies have indicated that adherence to dietary recommendations in kidney disease may be as low as 20%.[34,35] However, this review indicated that provision of medically-tailored meals (MTM) greatly improves adherence, providing another important tool to influence the treatment of chronic disease, in addition to addressing clinical and economic outcomes. Numerous studies have reported that provision of medically-tailored meals improved adherence to dietary recommendations in heart disease to greater than 90% of included patients.[36–49] Similarly, 100% of patients with diabetes who received medically-tailored nutrition were found to be adequately compliant, and 93% reported dietary satisfaction.[50–52] Findings among patients with chronic kidney disease were also similar.[53–57] Clearly, the provision of medically-tailored meals aids in adherence to dietary recommendations, helping patients overcome the barriers they face in adhering to complex dietary recommendations.

Improved adherence to dietary recommendations leads to numerous beneficial health outcomes which has been well documented by the literature presented in this review. Guidelines for the treatment of hypertension and heart failure recommend a reduced sodium diet, often referred to as the DASH diet.[8,27] Additionally, the Mediterranean diet has also shown benefit in cardiovascular risk reduction. Both Hikmet et al. and Davis et al. indicated that provision of medically-tailored meals following these dietary recommendations resulted in higher rates of controlled hypertension.[38,43] These interventions resulted in significant reductions in both systolic (3.3-12 mmHg reduction) and diastolic blood pressure (1.9–7.8 mmHg reduction).[36–44,58–60] In some cases, the prevalence of hypertension was reduced by 30%,[38] which is substantial considering 73 million Americans are diagnosed with hypertension.

These dietary interventions also resulted in impressive improvements in overall lipid panels, including reductions in LDL and total cholesterol as well as increases in HDL.[36,37,41,58,61] The impact of adherence to provided diets reduced lab values and resulted in reduced cardiovascular events, including stroke. These results illustrate the profound impact of adherence to

Table 8
Quality assessment of included articles.

Article	Methodical Quality	Applicability	Overall Effect
Anbar 2014	A	II	+ +
Aparicio 2013	A	I	+
Boespflug 2018	B	II	+
Brinkworth 2016	B	I	+ +
Camps 2017	A	III	+ +
Cardoso 2014	A	II	+ +
Casas 2014	A	I	+ +
Casas 2016	A	I	+ +
Castaner 2013	A	II	+
Collins 2017	B	I	0
Daly 2014	B	II	+
Davis and Bryan 2017	B	II	+ +
Davis and Hodson 2017	B	II	+
De Lorenzo 2017	A	II	+
Denissen 2017	B	II	+
Estruch 2018	B	I	+ +
Farrer 2014	B	III	+ +
Fito 2014	B	I	+
Friedman 2014	A	III	0
Goday 2016	B	I	+ +
Gomes-Delgado 2015	B	I	+
Goraya 2013	B	III	+ +
Gower 2015	A	III	+ +
Gu 2013	B	III	+
Haring 2014	A	I	+
Hikmat 2014	A	I	+ +
Hill 2015	A	II	+
Hummel 2013	B	II	+
Jenkins 2017	A	II	0
Johansson-Persson 2014	A	II	+
Juraschek 2017	A	I	+
Kent 2017	B	II	+ +
Kirwan 2016	A	II	+
Kitzman 2016	B	II	+
Martinez-Lapiscina 2013	B	I	+
McNamara 2018	A	I	+
Medina-Remon 2017	B	I	+ +
Mirfatahi 2016	B	II	+
Moorthi 2014	B	II	+
Ota 2016	A	II	+
Piccoli 2016	B	I	+ +
Reidlinger 2015	A	I	+
Richard 2013	B	III	+
Richard 2014	A	II	+
Roussel 2014	A	II	+
Ruscica 2016	A	II	+ +
Sanchez-Villegas 2013	B	I	+
Sayer 2015	A	II	+ +
Scott 2017	B	II	+
Tabibi 2017	B	II	+
Tay 2014	B	I	+ +
Toledo 2013	B	I	+
Urbanova 2017	A	III	+
Valls-Pedret 2015	B	I	+
vor Arnim 2013	B	II	+
Wada 2015	A	III	0

Key for Table:
Methodological Quality
A Least Bias; results are valid.
B Susceptible to some bias, but not sufficient to invalidate the results
C Significant bias that may invalidate the results

Applicability
I Sample is representative of the target population. It should be sufficiently large to cover both sexes, a wide age range, and other important features of the target populations (e.g., diet).
II Sample is representative of a relevant subgroup of the target population, but not the entire population.
III Sample is representative of a narrow subgroup of subjects only, and is of limited applicability to other subgroups.

Overall Effect
+ + Clinically meaningful benefit demonstrated
+ A clinically meaningful beneficial trend exists but is not conclusive.
0 Clinically meaningful effect not demonstrated or is unlikely.
- Harmful effect demonstrated or is likely

Table 9
The economic impact of food provision studies.

Systematic Review Clinical Outcome	Clinical Impact from the Literature	Cost from the Literature	Projected Cost Savings
Improvement in HTN through the DASH and MD diet adherence • SBP reduction: 3.3–12 mmHg,[36–43,58–60] higher starting SBP had greater reductions[60] • DBP reduction: 1.9–7.8 mmHg[36–38,40–44] • Higher rates of controlled HTN in patients: ○ Overall[38,42] ○ with MetS (OR = 9.5, DASH: 67%, control: 17%)[38] ○ without MetS (OR = 7.7, 57% vs. 15%)[38] • Reduce prevalence of HTN by 30%[38] CV event reduction with MD adherence • Difference of 3.1 CV events/1000 person-years (27.7% reduction)[62] • Difference of 1.8 stroke events/1000 person-years (30.5% reduction)[62] • Improved Framingham Risk Score (−0.19–0.42% reduction)[45] Adherence to dietary recommendations in heart disease • DASH >90%[38–40,44–46] • DASH 74–84%[58] • MD ≥ 95% or higher in the MD arm[36,37,41–43,47–49,61,62]	• 73 million Americans have HTN[2] • BP <130/80 vs <140/80: 21% reduced risk of major CV events (death, MI, HF, stroke)[97] • Every 20 mmHg increase in SBP >115/70 mmHg: increased risk for CV events by 29.2%[97] • 400,000 cardiovascular events could be prevented over 10 years if patients were adherent to DASH diet[98] • Reducing average population sodium intake to 2300 mg/day (which would be included a DASH diet), would reduce prevalence of HTN by 13%[99]**CV Outcomes Incidence:** • 795,000 Americans have a stroke annually[2] • 735,000 Americans have a heart attack annually[2]	**Cost of High BP:** • Workers with high BP have 31.6% or $1378 higher medical costs per year[100] **Costs of MI and HF:** • 3-year cost of MI = $73,300[67] • Average hospitalization cost = $20,246[101] • Lifetime costs: ○ Severe heart attack = $1 million[102] ○ Less severe = $760,000[102] • HF annual cost = $20,245 or $20,618[103] (severe cases = $40,000 annually) [calculated = $60,735–$120,000 across 3 years] **Costs of Stroke:** • 3-year cost of stroke = $71,600[67] • Average hospitalization cost = $20,396 ± $24,256[104] • Ischemic stroke with a secondary diagnosis of ischemic heart disease = $9836 higher than without ischemic heart disease ($p < 0.001$)[104]	More patients are likely to achieve the HTN control. A 21% reduction in CV events[97] could result in: • 154,350 fewer MI annually (saving $11.3 billion across 3 years or $3.8 billion annually) • 166,950 fewer strokes annually (saving $12 billion across 3 years or $4 billion annually) A 30.5% reduction in strokes could result in: • 242,475 fewer strokes annually • Cost savings of $4.9 billion annually • Cost savings of $17.4 billion over 3 years Cost savings over 10 years with adherence to DASH[98]: • Hospitalizations: $8.1 billion • Direct/indirect costs: $304–400 billion, depending on severity of the heart attack Cost savings by reducing prevalence of HTN: • 13% = $18 billion & 312,000 QALYS (=$32 billion annually)[99] • 30% = $24.9 billion in healthcare dollars savings
Lipid improvements with DASH and MD adherence • LDL reduction: ○ 5.2–10%[36,61] ○ 11.7–44.2 mg/dL[37,58] • TC reduction: 18.4–39.1 mg/dL[37] or − 4.8%[61] • HDL increase: 2.6–7.5 mg/dL[37,41]	• A reduction in LDL-C of 1 mmol/L (38.6 mg/dL) = 25% relative reduction in CV risk at 1 year[105]		
Weight loss or resolution of MetS with DASH or MD diet adherence • Body composition changes: ○ 0.8–9 kg weight loss[37,44,45,63] ○ 1.1–7.2 cm waist reduction[37,44,45,63] ○ 0.3–0.9 kg/m^2 BMI reduction[37,44] ○ 1.1% body fat reduction[44] • ≥5% weight loss, and every 1% of weight lost[58]: ○ 39% increase in the odds of resolving MetS in weight loss phase ○ 88% increase in the odds of resolving MetS in normal life • Reduced severity of MetS[44]	• 34.2% of the US population has MetS[106] (over 111 million people)	**Cost of MetS:** • 20% higher ($40,873 vs. $33,010, $p < 0.001$) in Medicare patients[107]	Resolution of MetS saves $7863 per patient per year. With 111 million patients diagnosed, decreasing MetS by 39% could result in: • $340.4 billion annually
A1c reduction with low carbohydrate and low calorie diet adherence[50–52,64] • 0.9–2.6% reduction	• 30.3 million Americans with DM and 84.1 million have pre-diabetes[2] • 15.8% of patients have an A1c >9% at a given time[108] • Improving A1c control (from 13.2% of patients with A1c >9% to 9.2%) reduced hospitalization days by 2% annually[65]	**Costs of DM:** • Annual medical cost = $9600/year[110] • Lifetime direct medical costs in the working population:	More patients are likely to lower A1c, particularly below 9% Improving A1c control to <9%[65] would result in:

(continued on next page)

Table 9 (*continued*)

Systematic Review Clinical Outcome	Clinical Impact from the Literature	Cost from the Literature	Projected Cost Savings
Adherence to diets in DM[50–52] • Adequate/compliant or 100%, with 93% dietary satisfaction	• DASH diet leads to a 69% reduction in T2DM incidence (OR 0.31)[109]	○ $84,000 in men ages 55–64 ○ $85,200 in women ages 55–64. ○ $124,700 in men ages 25–44 ○ $130,800 in women ages 25–44 **Improved Management Savings:** • 0.4% A1c reduction, cost savings per patient were (due to lower complications)[111]: ○ £1280 if A1c is at 7.5% ○ £2223 if A1c is at 8–9%	• 800,000 hospital days • $1.8 billion saved annually in the US Assuming a 1.5% reduction in A1c,[111] the cost savings would be: • $3840–$6669 per person • $11.6–20 billion in savings to the healthcare system If 58 million Americans are prevented from progressing to DM2, lifetime cost savings would range from $480–723 billion
Adherence to the DASH diet in HF • Excellent[59]	• DASH diet adherence in HF led to: ○ 16% reduction in 30-day readmissions[68] ○ 38 day shorter length of stay[68]	**Heart Failure Hospitalization Costs:** • Mean per-patient cost of a HF-related hospitalization = $14,631[112]	More patients are likely to be >90% adherent. Reducing HF readmissions by 16%,[68] would result in cost savings of: • $234,096 per 100 heart failure patients Reducing length of stay from 55 days to 17 days,[68] would result in cost savings of: • $79,425 per patient
Adherence to recommended dietary intake in CKD • Compliant[53–57] • Significantly lower mortality rates (0.44 (0.36–0.54)[53] • Patients with GFR ≤ 15 mL/min[53]: ○ 50% dialysis-free for 2 years ○ 25% dialysis free for 5 years • 2 year calculated costs savings[53]: ○ 80.6–94.3% per 100 patients • Stable GFR and less kidney injury[85]	• 660,000 patients in the United States with ESRD[113]	**CKD costs per person (Medicare)[114]:** • $1700 for stage 2 • $3500 for stage 3 • $12,700 for stage 4 • ESRD/Hemodialysis: $89,000	25–50% of ESRD patients are likely to be free from dialysis. Reducing the number of patients on dialysis would result in: • 25% free from dialysis for 5 years: $73 billion ($14.7 billion annually) • 50% free from dialysis for 2 years: $58.7 billion ($29.4 billion annually)

BP = Blood pressure, SBP = Systolic blood pressure, HTN = Hypertension, HF = Heart failure, MetS = Metabolic syndrome, A1c = Hemoglobin A1c, DM = Diabetes, CKD = Chronic kidney diease, ESRD = End stage renal disease.
DASH = Dietary Approaches to Stop Hypertension diet, MD = Mediterranean diet.

dietary recommendations. As patients were enabled to follow guideline-directed dietary interventions, patients experienced improvements in key risk factors for cardiac complications, including improvements in blood pressure and lipid control. While previous literature has documented the benefits of blood pressure and lipid reductions, the impact of dietary adherence is illustrated in the significant reduction of cardiovascular events.

Dietary adherence also is challenging in diabetes management. Recommended diabetes self-care practices nearly always include dietary recommendations with current guidelines recommending all diabetic patients be referred for personalized nutrition therapy..[26] A key goal of nutrition therapy is achieving and maintaining an appropriate body weight. Medically-tailored meals resulted in significant reductions in weight, waist circumference, BMI and body fat percentage.[37,44,45,63] Of note, these dietary changes also resulted in reduced severity of metabolic syndrome as well as increased odds of resolution of this common condition. Additionally, provision of low carbohydrate and low calorie diets resulted in A1c reductions comparable to many prominent medication therapies, reducing A1c by 0.9–2.6%.[50–52,64] Improvements in A1c control impact many health outcomes including reductions in hospitalizations as well as microvascular and macrovascular complications.[65,66] This novel approach to nutrition where healthcare professionals provide meals to patients is promising with documented improvements in A1c and weight control, offering a new mode of treatment to prevent and/or minimize progression and complications of diabetes.

Patients with chronic kidney disease are often asked to follow complex dietary restrictions, including reduced salt and protein intake. In addition, these patients often suffer from other comorbidities including hypertension and diabetes, complicating their dietary needs even further. This review indicated that provision of medically-tailored meals can overcome this barrier and ultimately delay progression of disease. Piccoli et al. indicated that providing nutrition that followed dietary recommendations aided in delay of progression to dialysis even in patients with GFR less than 15. In this study, 50% of patients remained dialysis-free after 2 years, and further, 25% were still dialysis free after five years.[53] This finding is significant, as dialysis imposes a heavy burden on both the patient and the healthcare system. The benefit of meal provision is further demonstrated in this study by significant decreases in mortality rates in patients receiving medically-tailored nutrition.

While the benefit of medically-tailored meals is clear in terms of health outcomes, the economic implications are harder to quantify. Improvements in key health markers, such as decreases in blood pressure and A1c, most often lead to improvements in health outcomes, including decreases in cardiovascular events or other complications. Costs of these complications are high with the average three-year cost of an MI or stroke ranging from

$71,600–$73,300.[67] The cost savings associated with reduction in cardiovascular events and strokes can range from $3.8 – $4.9 billion annually. While it cannot be assumed that medically-tailored meals will directly result in these cost savings, these costs certainly illustrate the potential economic impact of simple lifestyle improvements.

Meal provision represents a novel approach to chronic disease therapy with the potential for impressive implications for health outcomes and economic savings. Just as evidence-based medications and therapies are selected and covered by both commercial and private insurance, medically-tailored meals could be considered as a reimbursable service for patients with chronic disease, as further evidence builds regarding the impact of nutrition on health outcomes. In addition, the coverage of these services may represent an avenue for cost savings for insurance companies as healthcare costs continue to increase due to the burden of chronic disease.

When patients adhere to lifestyle changes, there are substantial patient clinical benefits as well as economic benefits. With costs in the healthcare system still rising, how do we position patients for better adherence and observe better clinical and economic outcomes? An excellent example from the literature that was published after the closure of the systematic review time period illustrates this point. Hummel and colleagues (2018) randomly distributed HF patients at discharge to usual care or HF-appropriate delivered meals. Even though the differences between groups were not significant, at 12 weeks, patients who received meals had improved cardiomyopathy clinical summary scores, fewer HF readmissions (11% vs 27% in the control group), and fewer days of rehospitalization (17 vs 55 days for the control group).[68] While limited inferences can be done from this short-term study due to its non-significance, this could be an area for further exploration.

5. Limitations

This review does have several limitations. While all included studies did provide some element of the subjects' diets, studies regarding complete meal delivery are rare. Many of these studies required patients to prepare their own meals and measured dietary intake based on dietary recall. This indicates that actual dietary intake may have varied from that which was reported. Secondly, many potentially relevant studies were excluded because meals were not directly provided by the researchers. Many other studies investigating the impact of diet and nutrition on economic and health outcomes were not included due to the observational nature of their design. Additionally, only studies written in the English language were included in the review, which could introduce bias, as key studies with positive or negative findings could be missed. Lastly, cost was not directly evaluated in the included studies. To date, there are few studies that quantify the costs associated with medically-tailored meals compared to the financial implications of nutrition on health outcomes. This review sought to investigate the economic impact of meal provision by comparing the improvements in health to the known costs of chronic disease. While this is not a direct representation of the true cost of meal delivery versus cost-savings in terms of health outcomes, it illustrates the potential benefit of medically-tailored meals and the need for further study in this area.

6. Conclusion

It is easier and less costly to prevent disease-based complications and progression than to manage acute issues. The healthcare system and healthcare professionals need to consider evolving strategies to empower patients to be part of the solution. Many Medicare Advantage and private insurance plans are beginning to cover medically-tailored meals, and with expanded access and a consistent structure, more data will be available to study the impact of dietary adherence on patient clinical and economic outcomes. What is clear is that providing medically-tailored meals to patients with chronic disease needs results in improved adherence, and when patients are adherence, clinical outcomes improve.

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