

Fakultät Gesundheits- und Pflegewissenschaften  
Studiengang Gesundheitsmanagement

# **Bachelorthesis**

**Die Anwendung der ketogenen Ernährungsform zur Gewichtsreduktion  
bei Adipositas und Präadipositas im Erwachsenenalter – eine  
systematische Übersichtsarbeit**

Erstgutachter: Prof. Dr. phil. Martin Grünendahl  
Fakultät Gesundheits- und Pflegewissenschaften

Zweitgutachter: Jennifer Petzsch, M. Sc.  
Fakultät Gesundheits- und Pflegewissenschaften

vorgelegt von: Lena Heutehaus  
Matrikel-Nr.: 39848  
Seminargruppen-Nr.: 182232

# Inhaltsverzeichnis

I Abbildungsverzeichnis .....	IV
II Formelverzeichnis .....	IV
III Tabellenverzeichnis .....	IV
IV Abkürzungsverzeichnis .....	V
V Gender-Disclaimer .....	VI
1 Einleitung .....	1
2 Theoretischer Hintergrund .....	2
2.1 Übergewicht und Adipositas .....	2
2.1.1 Epidemiologie .....	2
2.1.2 Messmethoden .....	3
2.1.2.1 Body-Mass-Index.....	3
2.1.2.2 Weitere Messmethoden.....	4
2.1.3 Klassifikation.....	4
2.1.4 Therapie .....	5
2.1.4.1 10 Regeln der DGE .....	6
2.1.4.2 Evidenzbasierte Leitlinie der Adipositastherapie .....	6
2.1.4.3 Ernährungstherapie .....	7
2.1.4.4 Weitere Therapieansätze.....	8
2.2 Ketogene Diät.....	10
3 Fragestellung .....	13
4 Methodik .....	14
4.1 Systematische Literaturrecherche .....	14
4.2 Rechercheprinzip.....	14
4.3 Suchkomponenten.....	15
4.4 Synonyme Suchbegriffe.....	16
4.5 Datenbanken .....	17

4.6 Suchstrings .....	18
4.7 Ein- und Ausschlusskriterien .....	24
4.8 Darstellung der Literaturrecherche – PRISMA.....	26
5 Ergebnisse.....	28
5.1 Einbezogene Studien.....	28
5.2 Studienergebnisse .....	37
6 Diskussion .....	39
6.1 Ergebnisbewertung.....	39
6.2 Methodenkritik .....	41
7 Fazit.....	42
VI Literaturverzeichnis .....	VII
VII Eidesstattliche Erklärung.....	IX
VIII Anhang: Artikel .....	X

## I Abbildungsverzeichnis

Abbildung 1: PRISMA Flussdiagramm .....	26
---	----

## II Formelverzeichnis

Formel 1: Berechnung des Body-Mass-Index.....	3
---	---

## III Tabellenverzeichnis

Tabelle 1: Klassifizierung des BMI.....	5
Tabelle 2: Kohlenhydratarme Diäten .....	11
Tabelle 3: Suchkomponenten der Literaturrecherche .....	15
Tabelle 4: synonyme Suchbegriffe der Literaturrecherche .....	16
Tabelle 5: Datenbankrecherche in MEDLINE via PubMed .....	20
Tabelle 6: Datenbankrecherche in DOAJ .....	21
Tabelle 7: Datenbankrecherche in BASE .....	22
Tabelle 8: Datenbankrecherche in LIVIVO .....	23
Tabelle 9: Datenbankrecherche in Cochrane Library .....	24
Tabelle 10: Ein- und Ausschlusskriterien Schritt 1.....	25
Tabelle 11: Ein- und Ausschlusskriterien Schritt 2.....	25

## IV Abkürzungsverzeichnis

BMI	- Body-Mass-Index/ Körpermasseindex
cm	- Zentimeter
DAG	- Deutsche Adipositas-Gesellschaft
DGE	- Deutsche Gesellschaft für Ernährung
DOAJ	- Dictionary of Open Access Journals
inkl.	- inklusive
kcal	- Kilokalorien
kg	- Kilogramm
LC	- Low-Carb
LCHF	- Low-Carb-High-Fat
LCKD	- Low-Carb Ketogenic Diet
LF	- Low-Fat
LFD	- Low-Fat Diet
m	- Meter
MEDLINE	- Medical Literature Analysis ans Retrieval System Online
O	- Orlistat
Tab.	- Tabelle
WHO	- World Health Organisation
WHR	- waist-to-hip-ratio

## V Gender-Disclaimer

Aus Gründen der besseren Lesbarkeit, wird in dieser Arbeit das generische Maskulinum verwendet. Es wird ausdrücklich darauf hingewiesen, dass sowohl das weibliche Geschlecht, als auch weitere Geschlechtsidentitäten gleichermaßen angesprochen werden.

# 1 Einleitung

Fettstoffwechselstörung, Hypertonie, Glukoseintoleranz, Diabetes Mellitus, koronare Herzkrankheit etc. – die Liste der möglichen Folgen einer Adipositas ist lang und besorgniserregend. Bei der Betrachtung aller Todesfälle von Brust- und Darmkrebs, ischämischer und hypertensiver Herzerkrankungen, Schlaganfall und Diabetes mellitus, starben 2014 in Deutschland allein 32.383 von gesamt 217.631 Menschen, d. h. rund 15 Prozent, bedingt durch eine vorab entwickelte Adipositas (Statista, 2016b). Zudem treiben Übergewicht und Fettleibigkeit die Ausgaben des Gesundheitssystems in die Höhe: Im Jahr 2015 wurden deutschlandweit neben 29,39 Milliarden Euro für direkte Kosten, sprich „alle mit der Kasse abgerechneten Leistungen inkl. Krankengeld, Rehabilitation, Pflegekosten, Unfallkosten“ (Statista, 2016a), 33,65 Milliarden Euro für indirekte Kosten, d. h. für „Arbeits- bzw. Produktivitätsausfälle, Arbeits- und Erwerbsunfähigkeit sowie vorzeitiges Versterben“ (Statista, 2016a) ausgegeben. Um diesen zahlreichen Todesfällen und den verursachten Kosten entgegenzuwirken, stehen im Rahmen der Adipositas-Therapie mehrere Ansätze zur Verfügung. Neben einer gesteigerten körperlichen Aktivität, ist es unabdingbar, das Ernährungsverhalten anzupassen. Die gängigste Therapie basiert auf einer konventionellen, fettarmen Diät, kombiniert mit ausreichend Bewegung (DGE, 2017). Die Zahl der vorhandenen Ernährungsformen bzw. Diäten und Programmen zur Gewichtsreduktion ist dennoch nahezu unüberschaubar – unter ihnen, der Ansatz einer kohlenhydratreduzierten, protein- und fettreichen Ernährungsweise. Die These der Atkins-Diät (Vertreter der benannten Ernährungsform) besagt, dass „der Adipositasentwicklung eine Störung des Kohlenhydratstoffwechsels zugrunde läge; die Gewichtsabnahme wird daher hauptsächlich durch eine Einschränkung der Kohlenhydratzufuhr angestrebt“ (Zunft, 2011). Ob diese Form der Ernährung einer Adipositastherapie gerecht werden kann oder sich gar als wirksamer herausstellt, gilt es, in der vorliegenden Arbeit zu untersuchen.

## 2 Theoretischer Hintergrund

### 2.1 Übergewicht und Adipositas

Adipositas wurde von der Weltgesundheitsorganisation (WHO) als eine „chronische Krankheit mit eingeschränkter Lebensqualität und hohem Morbiditäts- und Mortalitätsrisiko, die eine langfristige Betreuung erfordert“, eingestuft (WHO, 2001, S. 6). Sie beschreibt die Entwicklung einer „über das physiologische Maß hinausgehende Zunahme des Körperfettgewebes“ (Leitzmann et al., 2009, S. 288; WHO, 2001, S. 6) bei dem Menschen. Wird der BMI von  $25 \text{ kg/m}^2$  überschritten, liegt Präadipositas (Übergewicht) vor; bei einem BMI von über  $30 \text{ kg/m}^2$  wird von Adipositas (Fettleibigkeit) gesprochen (Leitzmann et al., 2009).

#### 2.1.1 Epidemiologie

Weltweit hat sich die Zahl der Übergewichtigen und Adipösen seit 1975 fast verdreifacht: 2016 zählten 1,9 Milliarden Erwachsene als übergewichtig; daraus resultiert ein Anteil von rund 39 Prozent Übergewichtigen bezogen auf die gesamte Bevölkerung. Unter den genannten Präadipösen sind weitere 650 Millionen Personen adipös. Mittlerweile sterben in zahlreichen Ländern mehr Menschen an Übergewicht und Adipositas, als an Untergewicht und Mangelernährung. (WHO, 2021)

Bei Betrachtung der Bundesrepublik Deutschland zeigt sich ein ähnliches Bild: Im Jahr 2015 wurden laut der Studie „Gesundheit in Deutschland aktuell“ (GEDA) 46,7 Prozent der Frauen und 61,6 Prozent der Männer als mindestens übergewichtig eingestuft (Schienkiewitz A, Mensink GBM, Kuhnert R et al., 2017). Etwa ein Drittel beider Gruppen weist einen BMI von über  $30 \text{ kg/m}^2$  auf und ist damit adipös (Schienkiewitz A, Mensink GBM, Kuhnert R et al., 2017). Damit ist „die Prävalenz von Übergewicht einschließlich Adipositas in den letzten Jahren unverändert hoch“ (Schienkiewitz A, Mensink GBM, Kuhnert R et al., 2017, S. 21).

## 2.1.2 Messmethoden

### 2.1.2.1 Body-Mass-Index

Der BMI (Body-Mass-Index) ist eine international gültige und anerkannte Maßzahl zur Feststellung der Stoffwechselerkrankung.

$$BMI = \frac{\text{Körpergewicht (kg)}}{\text{Körpergröße (m)}^2}$$

*Formel 1: Berechnung des Body-Mass-Index (eigene Darstellung)*

Beispiel: Eine Person wiegt 105 kg und misst 1,80 m.

$BMI = \frac{105 \text{ kg}}{1,80 \text{ m}^2} = 32,41 \rightarrow$  Diese Person weist eine Adipositas Grad I auf (Tab. 1).

Der BMI korreliert zumeist zu 95 Prozent mit dem Körperfettanteil des Menschen und ist daher die geeignete Methode zur Diagnose von Untergewicht, Normalgewicht oder Übergewicht und Adipositas (Benecke & Vogel, 2003).

Limitiert wird die Anwendung des BMI durch die fehlende Berücksichtigung der Körperzusammensetzung. Somit können sehr muskulöse Personen einen ebenso hohen BMI, wie übergewichtige und adipöse Personen aufweisen. Schließlich gilt situationsbedingt die genaue Messung der Körperzusammensetzung: „Ein Körperfettgehalt von 12 – 20 Prozent bei Männern und von 20 – 30 Prozent bei Frauen gilt als normal“ (Abernathy & Black, 1996, S. 448). (Leitzmann et al., 2009)

Ergänzend gibt der Taillenumfang Auskunft darüber, ob bereits Übergewicht vorliegt. Bei Frauen sollte die Taille nicht mehr als 88 cm und bei Männern nicht mehr als 102 cm umfassen. Grundsätzlich wird geraten, den Taillenumfang ab einem BMI von über 25 kg/m<sup>2</sup> zu messen. (WHO, 2001)

### 2.1.2.2 Weitere Messmethoden

Das Relativgewicht nach Broca war in der Vergangenheit die gebräuchlichste Kennzahl. Sie berechnete das (Körpergewicht (kg)\*100) / (Körperlänge (cm) – 100). Anhand dieser Rechnung wurden jedoch kleine Personen häufig und große Personen sehr selten als übergewichtig eingestuft. Aufgrund dessen wird von der Anwendung dieser Kennzahl gegenwärtig abgeraten. (Leitzmann et al., 2009)

Die bioelektrische Impedanzanalyse (BIA) ist eine moderne Methode zur Schätzung des etwaigen Körperfettanteils. Jedoch ist diese Anwendung ungeeignet für extrem adipöse Menschen sowie zur Messung kurzfristiger Veränderungen. (Benecke & Vogel, 2003)

Die Messung der Hautfaltendicke ist weiterhin eine Methode zur Schätzung des Körperfettanteils, jedoch sehr ungenau und schlecht reproduzierbar (Benecke & Vogel, 2003).

Das „vollständige Wiegen unter Wasser“ gilt zwar als Goldstandard, ist aber mit hohen Kosten und einer hohen Strahlenbelastung in Verbindung zu setzen (Benecke & Vogel, 2003).

Für das Taille-Hüft-Verhältnis (Waist-to-Hip-Ratio) liegen ebenso, wie für den BMI, Grenzwerte vor: Männer sollten ihr WHR unter 1 und Frauen unter 0,85 halten (Benecke & Vogel, 2003).

### 2.1.3 Klassifikation

Das Klassifikationsschema der WHO zeigt, nach welchen BMI-Werten eine Person als untergewichtig, normalgewichtig oder übergewichtig eingestuft wird. Demnach geht der BMI mit unterschiedlich niedrigen bzw. hohen Risiken für Begleiterkrankungen einher.

## Klassifizierung des BMI

BMI ( $\text{kg}/\text{m}^2$ )	Kategorie	Risiko für Begleiterkrankungen
< 18,5	Untergewicht	niedrig für kardiovaskuläre Erkrankungen, erhöht für andere Krankheiten
18,5 – 24,9	Normalgewicht	durchschnittlich
25,0 – 29,9	Übergewicht (Präadipositas)	geringfügig erhöht
30,0 – 34,9	Adipositas Grad I	erhöht
35,0 – 39,9	Adipositas Grad II	hoch
= 40	Adipositas Grad III	sehr hoch

Tabelle 1: Klassifizierung des BMI (WHO, 2001)

### 2.1.4 Therapie

Adipositas bedarf grundsätzlich einer Behandlung. Bei Präadipositas muss für eine Therapie zugleich einer der folgenden Faktoren zutreffen:

- eine abdominale Fettverteilung (Bauchraum)
- eine übergewichtsbedingte Erkrankung
- großer psychosozialer Leidensdruck

Handelt es sich ausschließlich um Übergewicht, wird lediglich empfohlen, eine Gewichtszunahme zu vermeiden – eine Gewichtsreduktion wird in diesem Falle nicht empfohlen. (Benecke & Vogel, 2003)

Das Ziel jeder Adipositastherapie sollte eine langfristige Gewichtsabnahme darstellen. Diese geht mit einer grundlegenden Veränderung des Lebensstils einher: Neben einer gesteigerten Aktivität, ist das Anpassen des Ernährungsverhaltens unabdingbar. Bereits die Gewichtsabnahme von fünf Prozent des Ausgangsgewichtes, welches mindestens ein Jahr gehalten werden kann, stellt in vielen Fällen einen Erfolg dar und führt zur Risikominderung von Folgeerkrankungen. (Benecke & Vogel, 2003; Leitzmann et al., 2009)

Je nach Grad der Adipositas, fällt die Therapie unterschiedlich aus: Je höher der BMI und der damit verbundene Adipositas-Grad, desto wahrscheinlicher wird im Rahmen

der Therapie ein medikamentöser Einsatz oder gar ein operatives Verfahren. (Benecke & Vogel, 2003)

In den folgenden Abschnitten wird schwerpunktmäßig auf die Ernährungstherapie eingegangen sowie deren Standards vorgestellt.

#### 2.1.4.1 10 Regeln der DGE

Die Deutsche Gesellschaft für Ernährung (DGE) erstellte anhand wissenschaftlicher Studien folgende „10 Regeln“ des vollwertigen Essens und Trinkens zur Erhaltung des Gesundheitszustandes sowie zur Förderung der Leistung und des Wohlbefindens. Die Theorie ist sich einig, dass die Vorgaben der DGE einer erfolgreichen ernährungsbasierten Adipositas-Therapie zu Grunde liegen.

1. Lebensmittelvielfalt genießen
2. Gemüse und Obst – nimm „5 am Tag“
3. Vollkorn wählen
4. Mit tierischen Lebensmitteln die Auswahl ergänzen
5. Gesundheitsfördernde Fette nutzen
6. Zucker und Salz einsparen
7. Am besten Wasser trinken
8. Schonend zubereiten
9. Achtsam essen und genießen
10. Auf das Gewicht achten und in Bewegung bleiben

(DGE, 2017)

#### 2.1.4.2 Evidenzbasierte Leitlinie der Adipositastherapie

Die evidenzbasierte Leitlinie der Adipositastherapie wurde von der Deutschen Adipositas-Gesellschaft (DAG) und unter Mitarbeit weiterer Gesellschaften speziell für alle ärztlichen und nichtärztlichen Berufsgruppen des Bereichs Prävention und Therapie von Adipositas entwickelt. Zu ihnen zählen neben Ärzten u. a. Ökotrophologen und Diätassistenten.

Folgende Ziele verfolgt die Leitlinie:

- die Verbesserung der Wahrnehmung des Gesundheitsproblems Adipositas in Deutschland,
- Patienten und Therapeuten eine Orientierung zu dem vielseitigen Krankheitsbild bieten zu können und
- die Gewährleistung spezifischer Informationen zu Prävention und Therapiemaßnahmen für alle Akteure im Gesundheitswesen und in der Gesundheitspolitik

(Deutsche Adipositas-Gesellschaft e.V. et al., 2014)

Grundlegend stimmen die Ansätze der Leitlinie mit denen der DGE bzgl. der Ernährungstherapie und den weiteren Schritten in der Adipositas-Therapie überein.

(Deutsche Adipositas-Gesellschaft e.V. et al., 2014)

#### 2.1.4.3 Ernährungstherapie

Für eine langfristige Gewichtsabnahme ist eine Ernährungsumstellung bei Adipositas unumgänglich. Oftmals wird, nach den 10 Regeln der DGE, eine ausgewogene, dennoch kalorienreduzierte und fettarme Diät empfohlen. Daraus resultiert im Erfolgsfall ein Kaloriendefizit (Kalorienaufnahme < Kalorienverbrauch), welches zu einer Abnahme führt. Das Kaloriendefizit kann gleichzeitig durch erhöhte Aktivität vergrößert werden. (Benecke & Vogel, 2003; Leitzmann et al., 2009)

Dennoch wird betont, die Kalorienzufuhr nicht auf ein riskantes Minimum zu begrenzen und dem Prozess der Gewichtsabnahme Zeit zu geben. Das Sättigungsgefühl nach einer Mahlzeit sollte in jedem Fall erreicht werden. Besonders niedrig-kalorische Diäten können ungesunde und teils riskante Folgen und Nebenwirkungen, wie Erschöpfung, Haarausfall, Schwindel, Blutdruckabfall oder gar die Entwicklung von Gallensteinen und eine Gallenblasenerkrankung nach sich ziehen. Die signifikante Abnahme von Gewicht in sehr kurzer Zeit sollte nur „bei dringend nötigem Gewichtsverlust vor Operationen“ (Benecke & Vogel, 2003, S. 19) und in ärztlicher Begleitung in Erwägung gezogen werden. (Benecke & Vogel, 2003)

Weiterhin hat sich, abseits der Empfehlungen der DGE, eine „energiereduzierte Mischkost mit verringertem Kohlenhydratgehalt und deutlich höherer Fettzufuhr“

(Leitzmann et al., 2009, S. 297) etabliert. Betont wird neben der Wahl von hochwertigen Fetten, wie etwa Olivenöl, der reichliche Anteil an Obst und Gemüse (Leitzmann et al., 2009). Diesen Ansatz gilt es in der vorliegenden Arbeit zu untersuchen.

Neben den gängigen Methoden gibt es zahlreiche „Reduktionsdiäten“, welche dem Körper jedoch mehr schaden, als helfen. Besonders für eine langfristige Abnahme und Stabilisierung des Gewichtes sind diese Diäten ungeeignet. Diese Ernährungsformen beabsichtigen zumeist eine starke Reduktion des Gewichtes in sehr kurzer Zeit und schließen dabei Lebensmittel oder ganze Lebensmittelgruppen aus bzw. ersetzen Mahlzeiten durch speziell entwickelte Produkte. Durch die eher kurzfristig ausgelegten Reduktionsdiäten folgt nach der Abnahme oftmals erneut die unerwünschte Gewichtszunahme. Dies wird „Jo-Jo-Effekt“ oder Weight Cycling genannt und ist zum einen demotivierend und zum anderen belastend für den Stoffwechsel. (Leitzmann et al., 2009)

Sogenannte „Light-Produkte“ können für Personen, welche auf nichts verzichten möchten, ebenso eine Hilfe darstellen. Seit Inkrafttreten der EU-Verordnung 1924/2006 über nährwert- und gesundheitsbezogene Angaben über Lebensmittel ist klar geregelt, unter welchen Umständen ein Produkt bspw. „leicht“, „fettarm“ oder „brennwertreduziert“ genannt werden darf.

Beispiel: Eine Packung Frischkäse (200 g) enthält im Durchschnitt 600 kcal. Ein „brennwertreduzierter“ Frischkäse muss sich an dieser Angabe orientieren und mindestens einen 30-prozentig geringeren Brennwert aufweisen – er darf maximal 420 kcal pro 200 Gramm enthalten.

#### 2.1.4.4 Weitere Therapieansätze

Neben einer Ernährungsumstellung als ersten Therapieschritt, sollten weitere Ansätze für einen möglichst großen Erfolg in der Adipositas-Therapie verfolgt werden. Es bedarf ergänzend einer körperlichen Aktivität und vermehrt Bewegung sowie einer Verhaltenstherapie. Bei vorangeschrittener Adipositas ist der Einsatz von Medikamenten oder auch eine Operation möglich bzw. notwendig. (Benecke & Vogel, 2003)

Bei einer gesteigerten Aktivität können Personen einerseits mit einer erhöhten Abnahme, andererseits mit der Zunahme an Muskelmasse (keine erhöhte Abnahme) rechnen. Beide Szenarien sind als positiv zu bewerten. Besonders bei dem Aufbau von Muskelmasse erhöht sich der Energiebedarf (Grundumsatz); die Aufrechterhaltung des Gewichtsverlustes wird dadurch gefördert. Gleichzeitig bleibt nach der Aktivität das Hungergefühl meist aus, woraufhin der Energieverbrauch nicht durch erneute Energieaufnahme mittels Nahrung kompensiert werden muss. Als geeignete Sportarten erweisen sich hierbei Walking, Jogging, Radfahren oder Schwimmen. Doch bereits eine gesteigerte Alltagsbewegung wirkt gesundheitsfördernd: Möglichkeiten bieten sich beim Treppensteigen oder beim Zurücklegen kurzer Strecken zu Fuß. Empfohlen wird ebenso die Integration von Kraftübungen, da bei reinem Ausdauer-Training anderenfalls zu Beginn Muskelmasse abgebaut wird. (Benecke & Vogel, 2003)

Verhaltenstherapien bestehen zumeist aus regelmäßigen Sitzungen über einen gewissen Zeitraum hinweg. Die Techniken umfassen hierbei die „Selbstbeobachtung und Aufzeichnung des Essverhaltens und der relevanten kognitiven und emotionalen Faktoren (Situationsfaktoren, Gedanken, Stimmungen und Gefühle, die vor, während und nach Versuchen zu wohlüberlegtem Essen und Sport auftreten). Eine Stimuluskontrolle umfasst eine Veränderung von Faktoren bzw. Auslösern, die zu unangemessenem Essen führen (Essen aus Langeweile, schnelles, hastiges Essen, Nebenher-Essen“ (Benecke & Vogel, 2003, S. 20). Zum besseren Umgang mit besagten Szenarien können beispielhaft ausreichende Zeitfenster zum Essen erstellt oder Methoden zum Umgang mit Frustration bzw. dem Entgegenwirken von „Frustessen“ entwickelt werden. Sporteinheiten sollten zudem unter Angabe des Ortes, der Zeit und der Dauer in einem Wochenplan festgehalten werden. Ein weiterer Baustein der Verhaltenstherapie besteht in einem Belohnungssystem für erfolgreich absolviertes Ess- und Bewegungsverhalten. Dies ist von Bedeutung, da durch den veränderten Lebensstil zumeist angenehme Tätigkeiten des Alltags wegfallen. Nicht zuletzt steht auch der Umgang mit sozialem Druck im Mittelpunkt einer Verhaltenstherapie: Wenn Misserfolge nicht bewältigt werden können, liegt ein Abbruch der Therapie nahe – dies gilt es zu verhindern. Mögliche Misserfolge können in Form von zu hohen Ansprüchen, durch zu großen Veränderungsaufwand oder durch nicht-rationales Befolgen von gefährlichen Hungerdiäten auftreten. (Benecke & Vogel, 2003)

Eine medikamentöse Therapie wird frühestens ab einem BMI von über 30 kg/m<sup>2</sup> (Adipositas), empfohlen. Sollten die vorangegangen Methoden jedoch Erfolg zeigen, entfällt die Notwendigkeit von Medikamenten. Unterschiedliche Wirkmechanismen können zu einem verstärkten Sättigungsgefühl, der reduzierten Aufnahme von Kohlenhydraten und Fetten oder der verhinderten Resorption von Fetten im Darm führen. Die Medikamente sollten nur zeitlich begrenzt, ergänzend zur Ernährungsumstellung und der Bewegungstherapie, eingenommen werden. (Benecke & Vogel, 2003)

Operative Maßnahmen werden erst bei einer stark ausgeprägten Adipositas (mindestens Grad III) empfohlen. Es braucht zudem einen motivierten Patienten, welcher willig ist, auch nach der Operation seinen Lebensstil zu ändern. Zumeist wird bei besagten Operationen eine Magenverkleinerung vorgenommen. Diese führt zu einer verminderten Maximalmenge an aufzunehmender Nahrung, wodurch ein Verzehr von großen Mengen zu Beginn anatomisch nicht mehr möglich ist. Verliert eine Person jedoch das Therapie-Ziel aus den Augen, kann sich der Magen erneut ausdehnen. Durch eine Operation kann innerhalb der ersten zwei Jahre ein Gewichtsverlust von 30 – 60 kg erzielt werden. Nachfolgend wird sich das Körpergewicht in der Regel im Bereich des Übergewichts eingependeln. Gefährdungen und Komplikationen einer derartigen Operation sollten immer berücksichtigt und abgeschätzt werden. Mit einer Wahrscheinlichkeit von 0,3 – 1,6 Prozent können bspw. eine Wundinfektion oder Lungenembolie auftreten. (Benecke & Vogel, 2003)

Festzuhalten ist, dass eine Adipositas-Therapie in jedem Fall darauf abzielen sollte, die Ernährungs- und Lebensweise grundsätzlich und damit langfristig zu verändern. Verhaltenstherapie, Medikation und Operation stellen kurz- bis mittelfristige Interventionen dar und haben einen vorrangig unterstützenden Charakter.

## 2.2 Ketogene Diät

Die ketogene Ernährungsform gehört in die Gruppe der kohlenhydratreduzierten Diäten und zeichnet sich durch eine fast ausschließlich protein- und fettreiche Ernährungsweise aus. Ziel der Diät ist der Status der Ketose (Stoffwechselleage). Erreicht wird diese durch ein längerfristiges Fasten oder die eingeschränkte Zufuhr von Kohlenhydraten. Im Körper findet im Folgenden ein vermehrter Abbau von Fettsäuren

zu sogenannten Ketonkörpern statt. Folglich steigen diese über den Normalwert des menschlichen Organismus hinaus und lösen die Glucose als Haupt-Energielieferanten ab. Zu beachten ist, dass bei der Adaption einer kohlenhydratreduzierten Ernährung, ausgehend von einer gewöhnlichen, kohlenhydratreichen Ernährungsweise, zu Beginn Nebenwirkungen, wie bspw. Kopfschmerzen, Müdigkeit oder die Minderung der Leistungsfähigkeit auftreten können. Diese klingen nach kurzer Zeit jedoch ab. (Leitzmann et al., 2009)

Pionier der Diät war Robert Coleman Atkins, seinerzeit Kardiologe und Ernährungswissenschaftler in Amerika. Seine weitverbreitete und bekannte Atkins-Diät soll maßgeblich zur Gewichtsreduktion beitragen. Atkins' These besagt, dass „der Adipositasentwicklung eine Störung des Kohlenhydratstoffwechsels zugrunde läge; die Gewichtsabnahme wird daher hauptsächlich durch eine Einschränkung der Kohlenhydratzufuhr angestrebt“ (Zunft, 2011). Diese Einschränkung beläuft sich auf maximal 20 bis 60 g Kohlenhydrate pro Tag (Zok, 2012). Dem Prinzip, welches gegenwärtig noch immer umstritten ist, folgten dennoch zahlreiche Nachahmer, wodurch die Entwicklung kohlenhydratärmer Diäten, genannt „Low-Carb-Diäten“, ihren Lauf nahm.

Neben der Atkins-Diät etablierten sich die South-Beach-Diät sowie die Punkte-Diät, welche ähnliche Verzehrvorgaben beinhalten:

### **Kohlenhydratarme Diäten**

Diät	Lebensmittelauswahl
Atkins-Diät	<ul style="list-style-type: none"> <li>- üppige Gerichte mit Fleisch, Fett, Käse, Eiern</li> <li>- abgelehnt: Brot, Zucker, Obst, Gemüse (außer Blattsalat)</li> <li>- Supplementierung von Vitaminen und Mineralstoffen</li> </ul>
South-Beach-Diät	<ul style="list-style-type: none"> <li>- bevorzugt: Fettzufuhr aus pflanzlichen Ölen, Fisch und Nüssen</li> <li>- Ablehnung von Weißmehl(-produkten) und Zucker</li> </ul>
Punkte-Diät	<ul style="list-style-type: none"> <li>- Lebensmittelauswahl nach Punkte-Schema: <ul style="list-style-type: none"> <li>o kohlenhydratreiche Lebensmittel: hohe Punktzahl</li> <li>o fett- und proteinreiche Lebensmittel: niedrige Punktzahl</li> </ul> </li> <li>- Begrenzung auf 60 Punkte pro Tag führt zu fettreicher Kost</li> </ul>

Tabelle 2: Kohlenhydratarme Diäten (Leitzmann et al., 2009)

Untersuchungen vergangener Jahre ergaben, dass „Adipöse mit Low-Carb-Diäten in den ersten sechs Monaten stärker abnehmen als mit fettarmen Diäten“ (Leitzmann et al., 2009, S. 306). Dies lässt sich vermutlich auf die begrenzte Lebensmittelauswahl und die damit einhergehende insgesamt geringere Nahrungsaufnahme zurückführen. Ergänzend führt der hohe Proteingehalt zu einem positiven Sättigungseffekt. (Leitzmann et al., 2009)

### 3 Fragestellung

Die vorliegende Arbeit verfolgt in erster Linie das Ziel, die Wirksamkeit der ketogenen Ernährungsform bei Übergewicht und Adipositas im Erwachsenenalter zu prüfen. Da Personen über sehr unterschiedliche Einstellungen, Präferenzen und Geschmäcker verfügen, soll die besagte Ernährungsform weiterhin als Alternative zu einer konventionellen Diät aufgezeigt werden. Nicht zuletzt muss das Problem der zahlreichen Adipositas-Fälle in Deutschland und weltweit in einem größeren Rahmen betrachtet werden. Mittels erfolgreicher Therapien, könnten einerseits durch Adipositas bedingte Kosten im Gesundheitswesen stark eingedämmt und andererseits Folgeerkrankungen bis hin zum Tod verhindert werden. Diese Aspekte führen zu der Hauptfragestellung dieser Arbeit:

*Führt die ketogene Ernährungsform zu einer Gewichtsreduktion bei übergewichtigen und adipösen Erwachsenen?*

Darüber hinaus wird untersucht, ob die ketogene Ernährungsform langfristige Erfolge im Rahmen einer Gewichtsreduktion erzielen kann und neben der Ernährungstherapie weitere Faktoren zur Gewichtsreduktion beitragen.

## 4 Methodik

Die Fragestellung dieser Arbeit wurde methodisch anhand einer systematischen Literaturrecherche bearbeitet. Recherchiert wurde in Fachdatenbanken zu den Themen Gesundheit und Medizin bzw. verwandter Fachbereiche. Das genaue Vorgehen der Recherche sowie die verwendeten Datenbanken werden im Nachfolgenden vorgestellt. Am Ende des vierten Kapitels werden die Schritte der Literaturrecherche sowie einzelne Komponenten, welche zur Auswahl der einbezogenen Studien führten, mithilfe eines Flussdiagramms zusammenfassend dargestellt.

### 4.1 Systematische Literaturrecherche

Eine systematische Literaturrecherche ist durch ein vorgegebenes Vorgehen gekennzeichnet und führt durch die Bearbeitung der einzelnen Schritte zu einer Übersicht der gesamten und relevanten Literatur im Hinblick auf ein ausgewähltes Thema. Ein bedeutender Part ist hierbei die Entwicklung eines Suchstrings. Dieser wird in verschiedenen Fach- und Metadatenbanken (abgewandelt) angewendet. Diese und weitere wichtige Schritte, die zum gesamten Ablauf der systematischen Literaturrecherche gehören, werden im Folgenden vorgestellt. (Nordhausen & Hirt, 2020)

### 4.2 Rechercheprinzip

Bei der systematischen Literaturrecherche ist ein sensitivs oder spezifisches Rechercheprinzip möglich. Das Rechercheprinzip wird in Abhängigkeit vom Umfang der Suche gewählt. In der vorliegenden Arbeit galt es, die vollständige und relevante Literatur zum Thema ausfindig zu machen, wodurch nur das sensitive Rechercheprinzip infrage kam. (Nordhausen & Hirt, 2020)

Das sensitive Rechercheprinzip wird durch die Verwendung vieler verschiedener Suchbegriffe und Synonyme gekennzeichnet. Zudem ist die Suche in verschiedensten, den Themenbereichen entsprechenden Fachdatenbanken zu empfehlen. Dieses Vorgehen liefert zahlreiche Treffer, welche auf Relevanz untersucht werden müssen.

Meist kommt schlussendlich nur ein kleiner Teil der zu Beginn erhaltenen Treffer in Frage. Der Prozess ist, vergleichend mit dem spezifischen Rechercheprinzip, aufwendiger und langwieriger, andererseits jedoch weniger anfällig für das Übersehen relevanter Studien. (Nordhausen & Hirt, 2020)

#### 4.3 Suchkomponenten

In diesem Schritt wird die Forschungsfrage in thematische Bestandteile, sogenannte Suchkomponenten, umgewandelt. Diese Komponenten ergeben ein recherchierbares Format für die einzelnen Fachdatenbanken und deren Eingabemasken. Auch für nachfolgende Schritte, wie der Identifizierung von synonymen Suchbegriffen, sind die Suchkomponenten von Bedeutung. (Nordhausen & Hirt, 2020)

Nach Bedarf gibt es für diesen Schritt vorgegebene Schemata, wie z. B. PICO, nach welchen u. a. gewünschte Studientypen ausfindig gemacht werden können. Die Anwendung dieser wird jedoch nicht im Vordergrund der Arbeit stehen, da vorrangig eine inhaltliche Suche und keine Suche nach bestimmten Studientypen stattfand. Dennoch wurde bei der Beurteilung der Studien ebenfalls auf Studientypen geachtet, um bspw. Bias ausschließen, und damit die Relevanz erhöhen zu können.

Folgende Suchkomponenten fanden für die vorliegenden Arbeit Anwendung:

#### Suchkomponenten der Literaturrecherche

Deutschsprachig	Englischsprachig
Adipositas	Obesity
Ernährung	Diet
Ketogen	Ketogenic
Gewichtsverlust	Weight loss
Erwachsene	adults

Tabelle 3: Suchkomponenten der Literaturrecherche (eigene Darstellung)

Zu berücksichtigen ist, wie viele und welche Suchkomponenten bei einer Recherche miteinbezogen werden. Abhängig davon, kann eine Suche zu „detailliert“ sein und möglicherweise keine Treffer erzielen. (Nordhausen & Hirt, 2020)

Im vorliegenden Beispiel wurden ausschließlich die Hauptkomponenten der Fragestellung in die Suche einbezogen, um eben benanntes Szenario ausschließen zu können.

#### 4.4 Synonyme Suchbegriffe

Synonyme Suchbegriffe bzw. Stichwörter werden von den Autoren und Autorinnen häufig und zentral verwendet und finden sich zumeist schon im Titel oder Abstract einer Publikation wieder. Aufgrund dessen ist es unabdingbar, im Rahmen der Recherche auch nach Synonymen zu suchen. (Nordhausen & Hirt, 2020)

Die gefundenen Stichwörter sollten hinsichtlich der Sprache an die verschiedenen Fachdatenbanken angepasst werden (Nordhausen & Hirt, 2020). Da in der vorliegenden Arbeit neben englischsprachigen Recherchen auch deutschsprachige durchgeführt worden, wurde diese Anpassung vorgenommen. Mittels eines Brainstormings wurden folgende Synonyme für die bestehenden Suchkomponenten gewählt:

#### Synonyme Suchbegriffe der Literaturrecherche

Suchkomponenten	Synonyme Suchbegriffe			
<i>Adipositas</i>	Präadipositas	Übergewicht	Fettleibigkeit	
<i>Ernährung</i>	Diät			
<i>ketogen</i>	kohlenhydratreduziert	keto	low carb	
<i>Gewichtsverlust</i>	Gewichtsreduktion	Abnahme		
<i>Erwachsene</i>				
<i>obesity</i>	adiposity	overweight	adipose	obese
<i>Diet</i>	nutrition			
<i>ketogenic</i>	low carbohydrate	low carb	carb reduced	keto
<i>weight loss</i>	weight reduction			
<i>adults</i>				

Tabelle 4: synonyme Suchbegriffe der Literaturrecherche (eigene Darstellung)

## 4.5 Datenbanken

Für eine systematische Recherche ist vorab die Festlegung der zu durchsuchenden Fachdatenbanken von Bedeutung. Dafür bedarf es einer Auseinandersetzung damit, welche Datenbanken thematisch relevant erscheinen und wie viele durchsucht werden sollen. Da das Ziel der vorliegenden Arbeit eine Übersicht aller relevanten Studien zum Thema darstellt, wurden alle thematisch relevanten Datenbanken durchsucht; es wurde sich auf keine bestimmte Anzahl begrenzt. Die thematische Relevanz der Fachdatenbanken wurde mithilfe des Manuals zur Literaturrecherche in Fachdatenbanken (Nordhausen & Hirt, 2020) identifiziert. Letzteres beinhaltet eine Übersicht der wichtigsten (Meta-)Datenbanken, u. a. der Bereiche Gesundheit, Medizin sowie Psychologie und gibt einen Einblick in die Themenschwerpunkte (Nordhausen & Hirt, 2020). Anhand dieser wurden die zu durchsuchenden Datenbanken ausgewählt. Folgende Themenschwerpunkte und damit einhergehende Datenbanken wurden in die Recherche einbezogen:

### Themenschwerpunkte:

- *Ernährung, Evidence-Based Health Care, Gesundheit, Gesundheitsbereich, Gesundheitsmanagement, Gesundheitsversorgung, Gesundheitswesen, Klinische Studien, Medizin, Pflege, Public Health etc.*

### Datenbanken:

- *BASE, Cochrane Library, DOAJ, DRKS, Epistemonikos, FIT-Nursing Care, Scopus, LIVIVO, MEDLINE etc.*

Folgende Themenschwerpunkte und damit einhergehende Datenbanken spielten keine Rolle und wurden ausgeschlossen:

### Themenschwerpunkte:

- *Demenz, Pädagogik, Bibliothekswesen, Ergotherapie etc.*

### Datenbanken:

- *ALOIS, DIE, LISTA, OTDBASE, OTseeker etc.*

Weiterhin galt es für die Recherche zu beachten, welche Publikationstypen die relevanten Datenbanken anbieten. Einbezogen wurden vorrangig: *RCTs, Primärstudien, Zeitschriftenartikel*

Ebenso als Literatur geeignet, jedoch nicht für die vorliegende Arbeit methodisch verwendbar, sind: *Leitlinien, systematische Übersichtsarbeiten, Open Access Bücher*  
Datenbanken mussten zudem ausgeschlossen werden, wenn die dazugehörige Literatur ausschließlich in nicht-englischer oder nicht-deutscher Sprache veröffentlicht wurde.

Nach den genannten methodischen und pragmatischen Kriterien (Nordhausen & Hirt, 2020) sowie weiteren themenspezifischen Untersuchungen, konnten in folgenden Datenbanken Treffer erzielt werden:

- MEDLINE, DOAJ, BASE, LIVIVO, Cochrane Library (Tab. 5-9)

## 4.6 Suchstrings

Die Entwicklung eines oder mehrerer Suchstrings ist der finale Schritt vor der Recherche. Der Suchstring führt die identifizierten Suchkomponenten der Fragestellung sowie die synonymen Suchbegriffe mithilfe der booleschen Operatoren zusammen. Letztere sind konkrete Suchbefehle, wodurch die einzelnen Parts des Suchstrings verknüpft werden können. Am häufigsten verwendet werden AND, OR und NOT. (Nordhausen & Hirt, 2020)

Folgende Bedeutung tragen die Operatoren:

- AND: die erhaltenen Treffer müssen sowohl Komponente A als auch Komponente B enthalten.
- OR: die erhaltenen Treffer müssen entweder Komponente A oder Komponente B enthalten.
- NOT: die erhaltenen Treffer dürfen ausschließlich Komponente A, nicht aber Komponente B enthalten.

(Nordhausen & Hirt, 2020)

In der Regel werden die Suchkomponenten innerhalb des Suchstrings mit AND, die synonymen Suchbegriffe mit OR verbunden. (Nordhausen & Hirt, 2020)

Aufgrund des datenbankspezifischen Aufbaus und verschiedener Suchmöglichkeiten, muss zumeist für jede Datenbank ein neuer Suchstring entwickelt werden. Gleichbleibend ist jedoch das Prinzip, stets alle Suchkomponenten in den Suchstring

einzuzeichnen. Andernfalls ist der Suchstring nicht mehr für die Beantwortung der Fragestellung geeignet. Es bietet sich dennoch an, den ursprünglich entwickelten Suchstring für weitere Datenbanken als „Probedurchlauf“ zu nutzen. Anhand dessen lässt sich schneller erkennen, ob der Suchstring zu detailliert oder zu grob gestaltet wurde. (Nordhausen & Hirt, 2020)

Im Folgenden werden sowohl die Suchstrings, als auch die Datenbanken und ihre Hintergrundinformationen zur Recherche vorgestellt. Auf Besonderheiten der Recherchen innerhalb der einzelnen Datenbanken wird näher eingegangen:

## MEDLINE

MEDLINE via PubMed ist eine fachdatenbankspezifische Suchmaschine und stellt überwiegend Primärartikel aus Fachzeitschriften der Bereiche Biomedizin und Gesundheit bereit (Nordhausen & Hirt, 2020). Die Oberflächen- und Suchsprache ist ausschließlich Englisch, woraufhin nur in dieser Sprache recherchiert wurde. MEDLINE bietet eine große Auswahl an Filtern, wodurch zum einen die Suchkomponente des Erwachsenenalters durch den Filter „age: 19+ years“ ersetzt werden konnte. Zum anderen beschränkte sich der Suchzeitraum auf die vergangenen 20 Jahre, um die aktuellsten Ergebnisse zu erhalten. Weiterhin wurde nur nach klinischen sowie randomisiert kontrollierten Studien gesucht, um Primärergebnisse zu erhalten. Anzumerken ist, dass, aufgrund der hohen Anzahl an Treffern, die zwei häufigsten, neben Adipositas erschienenen Krankheitsbilder – Diabetes und Krebs – über den booleschen Operator NOT ausgeschlossen wurden. Schließlich konnten 49 Treffer in MEDLINE erzielt werden (Tab. 5).

## Datenbankrecherche in MEDLINE via PubMed

<b>Datenbank</b>	MEDLINE via PubMed
<b>Anbieter</b>	U.S. National Institutes of Health's National Library of Medicine (NIH/NLM)
<b>Datum der Suche</b>	12.06.2021, 13:32
<b>Datenbankupdate</b>	tägliches Update
<b>Sprachen</b>	Englisch
<b>Suchzeitraum</b>	2001-2021
<b>Publikationstyp</b>	clinical trial, randomized controlled trial
<b>Filter</b>	text availability: (free) full text species: humans language: english, german age: 19+ years
<b>Suchstring</b>	((Diet, High-Protein Low-Carbohydrate"[Mesh]) OR ("Diet, Ketogenic"[Mesh]) OR keto* OR low-carb*) AND "weight loss" AND ("Adiposity"[Mesh] OR obesity OR obese OR adipose OR overweight) obes* NOT diabetes obes* NOT cancer
<b>Treffer</b>	49

Tabelle 5: Datenbankrecherche in MEDLINE via PubMed (eigene Darstellung)

## DOAJ

Das Directory of Open Access Journals (DOAJ) ist eine Fachdatenbank, welche frei zugängliche Fachzeitschriften und deren Inhalte aus sämtlichen Wissenschaftsbereichen bereitstellt (Nordhausen & Hirt, 2020). Die Oberflächen- und Suchsprache ist ausschließlich Englisch, woraufhin nur in dieser Sprache recherchiert wurde. DOAJ bietet keine Filter; es kann lediglich über den Suchstring recherchiert werden. Letzterer zeigte sich bei längerer und detaillierterer Ausführung als sehr empfindlich (kaum Treffer), weshalb der Suchstring eher kurz und offen gestaltet wurde. Die Komponente „ketogen“ bzw. „keto\*“ konnte von der Datenbank nicht erkannt oder verarbeitet werden, woraufhin nur „low carb\*“ verwendet wurde. Es konnten 52 Treffer erzielt werden (Tab. 6).

## Datenbankrecherche in DOAJ

<b>Datenbank</b>	DOAJ
<b>Anbieter</b>	Directory of Open Access Journals
<b>Datum der Suche</b>	07.06.2021, 10:33
<b>Datenbankupdate</b>	fortlaufend
<b>Sprachen</b>	Englisch
<b>Suchzeitraum</b>	-
<b>Publikationstyp</b>	-
<b>Filter</b>	-
<b>Suchstring</b>	low carb* (diet OR nutrition) (obesity OR obese OR adiposity OR adipose OR overweight) weigh* loss adults
<b>Treffer</b>	52

*Tabelle 6: Datenbankrecherche in DOAJ (eigene Darstellung)*

## BASE

Die Meta-Suchmaschine BASE der Universitätsbibliothek Bielefeld stellt vorwiegend Meta-Daten aus indexierten Quellen sämtlicher Wissenschaftsbereiche zur Verfügung (Nordhausen & Hirt, 2020). Die Recherche in BASE war sowohl englischsprachig, als auch deutschsprachig möglich. Aus dem deutschen Suchstring resultierten jedoch keine thematisch logischen Treffer, weshalb die Recherche in Englisch fortgeführt wurde. Da die Suchmaske auch Filter zur Verfügung stellt, wurde sowohl der freie Zugang der Dokumente ausgewählt, als auch der Publikationstyp als Artikel festgelegt. Zudem kam nur der Bereich „Medizin und Gesundheit“ der Dewey-Dezimalklassifikation für die Recherche in Frage. Es konnten 32 Treffer erzielt werden (Tab. 7).

## Datenbankrecherche in BASE

<b>Datenbank</b>	BASE (Meta-Suchmaschine)
<b>Anbieter</b>	Universitätsbibliothek Bielefeld
<b>Datum der Suche</b>	07.06.2021, 10:42
<b>Datenbankupdate</b>	täglich
<b>Sprachen</b>	Englisch, Deutsch
<b>Suchzeitraum</b>	-
<b>Publikationstyp</b>	Artikel
<b>Filter</b>	Zugang: Open Access Dokumentenart: Artikel Sprache: Englisch Dewey-Dezimalklassifikation (DDC): Medizin und Gesundheit
<b>Suchstring</b>	(keto* OR low carb*) (diet OR nutrition) (obesity OR obese OR adiposity OR adipose OR overweight) weigh* loss adults
<b>Treffer</b>	32
<b>Zusatz</b>	keine thematisch logischen Treffer bei deutschsprachiger Suche

Tabelle 7: Datenbankrecherche in BASE (eigene Darstellung)

## LIVIVO

LIVIVO, bereitgestellt durch das ZB MED – Informationszentrum Lebenswissenschaften, ist eine Meta-Suchmaschine, welche Literatur, Fakten- und Forschungsdaten u. a. aus den Bereichen Medizin, Gesundheitswesen und Ernährungswissenschaften, anbietet (Nordhausen & Hirt, 2020). Die Recherche in LIVIVO war sowohl englischsprachig, als auch deutschsprachig möglich. Die deutschsprachige Suche ergab jedoch keine Treffer innerhalb wissenschaftlicher Artikel. Über die Filterfunktion konnten alle Dokumente mit freiem Zugang angezeigt werden. Im Suchstring musste zudem der boolesche Operator NOT eingesetzt werden, da allein die Komponente „Adults/ Erwachsene“ offenbar nicht verarbeitet werden konnte – es wurden folglich alle Altersgruppen unter 18 Jahren ausgeschlossen. In LIVIVO konnten 13 Treffer erzielt werden (Tab. 8).

## Datenbankrecherche in LIVIVO

<b>Datenbank</b>	LIVIVO (Meta-Suchmaschine)
<b>Anbieter</b>	ZB MED – Informationszentrum Lebenswissenschaften
<b>Datum der Suche</b>	07.06.2021, 10:56
<b>Datenbankupdate</b>	datenbankabhängig
<b>Sprachen</b>	Englisch
<b>Suchzeitraum</b>	-
<b>Publikationstyp</b>	-
<b>Filter</b>	free access
<b>Suchstring</b>	(keto* OR "low carb*") (diet OR nutrition) (impact OR influence) (obesity OR obese OR adiposity OR adipose OR overweight) weigh* loss adults NOT infant* adults NOT child* adults NOT adolescence
<b>Treffer</b>	13
<b>Zusatz</b>	keine wissenschaftlichen Treffer bei deutschsprachiger Recherche

Tabelle 8: Datenbankrecherche in LIVIVO (eigene Darstellung)

## Cochrane Library

Die Cochrane Library von Cochrane/John Wiley & Sons ist eine Fachdatenbank, welche sich thematisch auf die Bereiche Medizin und Gesundheitsversorgung konzentriert. Neben systematischen Übersichtsarbeiten, stehen randomisierte und quasi randomisiert kontrollierte Studien im Mittelpunkt (Nordhausen & Hirt, 2020). Die Suche wurde ausschließlich in Englisch durchgeführt. Um die Abgrenzung zu den systematischen Reviews zu erhalten, wurde nur in dem Bereich der „Trials“ recherchiert. Aufgrund der hohen Anzahl an Treffern, wurde eine weitere Suchkomponente in den Suchstring aufgenommen: „Impact/ Influence“. Folglich konnten 63 Treffer erzielt werden (Tab. 9).

## Datenbankrecherche in Cochrane Library

<b>Datenbank</b>	Cochrane Library
<b>Anbieter</b>	Cochrane/John Wiley & Sons
<b>Datum der Suche</b>	07.06.2021, 11:18
<b>Datenbankupdate</b>	datenbankabhängig
<b>Sprachen</b>	Englisch
<b>Suchzeitraum</b>	-
<b>Publikationstyp</b>	Trials
<b>Filter</b>	-
<b>Suchstring</b>	(low-carbohydrate OR ketogenic OR keto* OR low-carb*) diet (influence OR impact) "weight loss" (adiposity OR obesity OR obese OR adipose OR overweight) adults
<b>Treffer</b>	63

Tabelle 9: Datenbankrecherche in Cochrane Library (eigene Darstellung)

## 4.7 Ein- und Ausschlusskriterien

Bei der Studienauswahl galt es, gewisse Ein- bzw. Ausschlusskriterien zu beachten – nicht jede Studie, welche aus einem Suchstring resultiert, ist relevant. Dies kann einerseits auf das methodische Vorgehen zurückgeführt werden oder aus technischen Ungenauigkeiten der einzelnen Datenbanken resultieren. Einige Kriterien ergeben sich bereits aus der Fragestellung der Arbeit; diese und weitere werden im Folgenden aufgelistet. Die Auflistung gliedert sich in zwei Schritte:

1. Kriterien der Studienauswahl beim Lesen des Titels und des Abstracts
2. Kriterien der erweiterten Studienauswahl beim Lesen des Volltextes

## Ein- und Ausschlusskriterien Schritt 1

Einschlusskriterien	Ausschlusskriterien
Menschen	Tiere
Alter > 18 Jahre (Erwachsene)	Alter < 18 Jahre
BMI > 25 kg/m <sup>2</sup> (Übergewicht/ Adipositas)	BMI < 25 kg/m <sup>2</sup>
Übergewicht/ Adipositas	Andere Erkrankung, z. B. Demenz
Primär-Outcome: Gewichtsreduktion	Anderes Primär-Outcome, z. B. Steigerung der Schlafqualität
Ketogene/ kohlenhydratreduzierte Diät	Andere Form der Diät, z. B. mediterrane Diät
Repräsentativ (Anzahl Teilnehmer)	Nicht repräsentativ (zu wenige Teilnehmer)

Tabelle 10: Ein- und Ausschlusskriterien Schritt 1 (eigene Darstellung)

## Ein- und Ausschlusskriterien Schritt 2

Einschlusskriterien	Ausschlusskriterien
Ketogene Diät im Sinne einer kohlenhydratreduzierten, protein- und fettreichen Diät	Diät entspricht nicht den Vorgaben einer ketogenen Diät
Kohlenhydrat-Anteil zu Beginn der Diät: < 20 g	Kohlenhydrat-Anteil zu Beginn der Diät zu hoch

Tabelle 11: Ein- und Ausschlusskriterien Schritt 2 (eigene Darstellung)

Die Mehrheit der durchgeführten Studien zur ketogenen Diät basiert auf dem Konzept, die Kohlenhydrat-Menge zu Beginn der Diät möglichst gering zu halten. In den folgenden Wochen oder Monaten wird diese dann allmählich gesteigert. Dieses Vorgehen kann mit dem der Atkins-Diät verglichen werden, wobei die Kohlenhydratzufuhr auf insgesamt 20 – 60 g pro Tag begrenzt ist (Zok, 2012). Für die vorliegende Arbeit bedeutet dies, Studien zu identifizieren, welche den Kohlenhydrat-Anteil zu Beginn auf 20 g täglich begrenzen, und im Laufe der Intervention optional erhöhen (Tab. 11).

## 4.8 Darstellung der Literaturrecherche – PRISMA

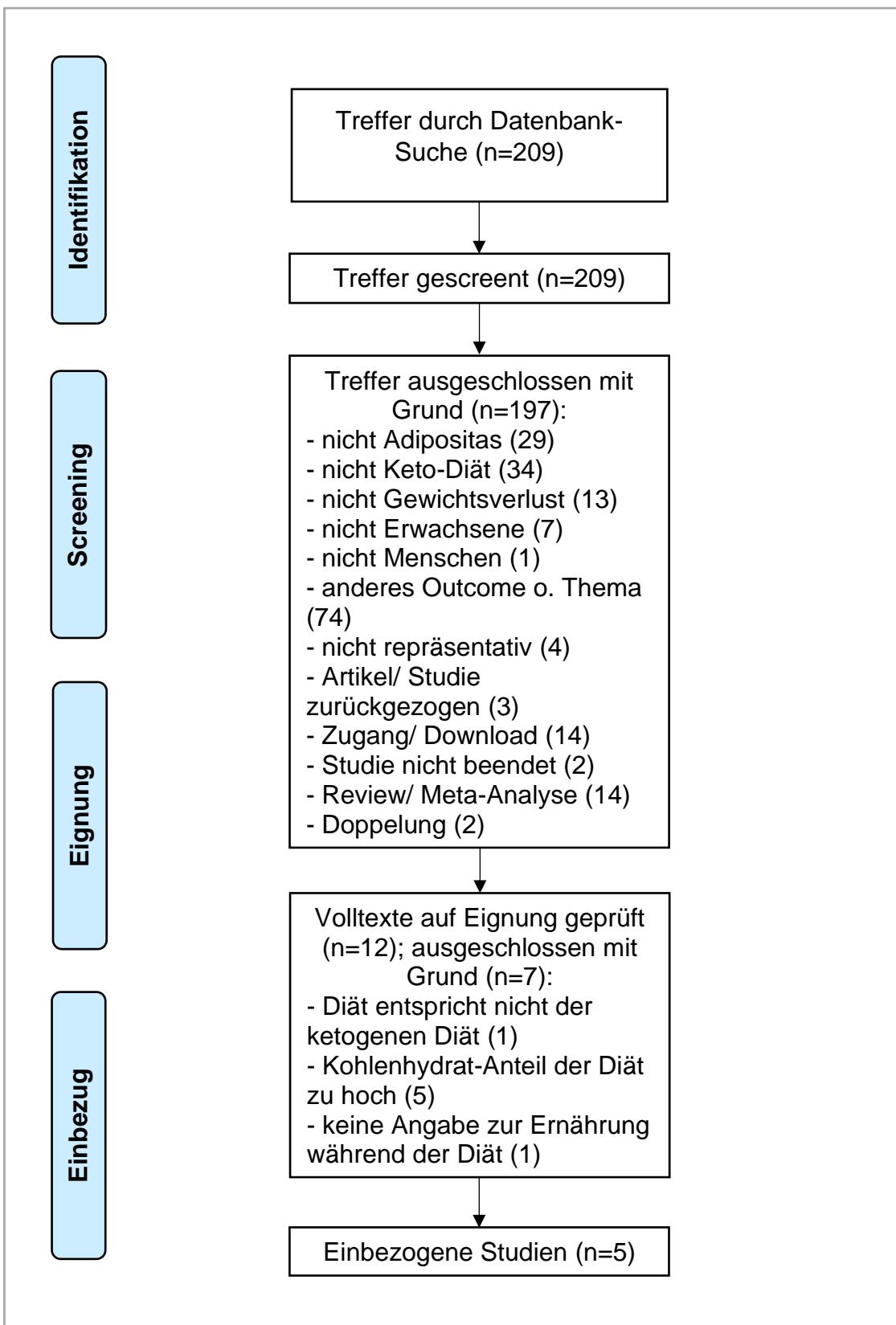


Abbildung 1: PRISMA Flussdiagramm (Moher et al., 2009)

Das PRISMA-Flussdiagramm gewährt einen Einblick in den Ablauf der systematischen Literaturrecherche und der Studienauswahl. Mithilfe der in Kapitel 4.6 vorgestellten Suchstrings konnten in den besagten Datenbanken 209 Treffer erzielt werden. Ausgehend von diesen, mussten jedoch 197 Ergebnisse nach dem Titel- bzw. Abstract-Screening ausgeschlossen werden. Die Grundlage hierfür bildeten die Ein- und Ausschlusskriterien sowie einzelne formabhängige Aspekte. Die verschiedenen Gründe sind in der Abbildung aufgelistet. Für die Volltext-Prüfung wurden demnach zwölf Treffer einbezogen; weitere sieben Studien wurden begründet ausgeschlossen (Abb. 1). In die vorliegende Arbeit konnten schließlich fünf Studien einbezogen werden.

## 5 Ergebnisse

Im ersten Teil dieses Abschnittes werden die gefundenen, als relevant eingestuften Studien vorgestellt. Hierbei wird besonders auf die kohlenhydratreduzierten Diäten der Studien eingegangen. Da die Vergleichs-Diäten nicht im Vordergrund dieser Arbeit stehen, werden ihre Inhalte lediglich am Ende des Kapitels 5.1 zusammenfassend erklärt.

Daraufhin erfolgt die Auswertung der Studienergebnisse unter Einbezug der Fragestellung dieser Arbeit.

### 5.1 Einbezogene Studien

#### Studie 1

Titel: „A Randomized Trial of a Low-Carbohydrate Diet vs Orlistat Plus a Low-Fat Diet for Weight Loss“

Autoren: Yancy, William S. Jr.; Westman, Eric C.; McDuffie, Jennifer R.; Grambow, Steven C.; Jeffreys, Amy S.; Bolton, Jamiyla; Chalecki, Allison; Oddone, Eugene Z.

Zeitschrift und Jahr: JAMA Internal Medicine (2010)

Der Hintergrund dieser Studie ist der Vergleich zweier möglicher Diät-Konzepte zur Gewichtsreduktion bei Übergewicht und Adipositas. Verglichen wurde eine kohlenhydratreduzierte, ketogene Diät (low-carbohydrate, ketogenic diet (LCKD)) mit dem Einsatz von Orlistat im Rahmen einer fettreduzierten Diät (orlistat + low-fat diet (O + LFD)). Orlistat ist ein Arzneimittel zur Behandlung von Adipositas. (Yancy et al., 2010)

Im Zeitraum von April 2005 bis Oktober 2006 wurden 525 Personen aus Ambulanzen in Durham, North Carolina, rekrutiert. Die Einschlusskriterien umfassten ein Alter von 18 – 70 Jahren und einen BMI von 27 – 30 kg/m<sup>2</sup> inklusive einer durch Adipositas bedingten Erkrankung oder einen BMI von 30 kg/m<sup>2</sup> oder höher. Zu den Ausschlusskriterien gehörten u. a. ein vorangegangener Gewichtsverlust, eine instabile Herzerkrankung, Demenz oder das Vorliegen einer Schwangerschaft. 160 Personen erfüllten die Einschlusskriterien, stimmten einer Teilnahme zu und wurden

demnach einer der zwei möglichen Diät-Gruppen randomisiert zugeordnet; 146 Personen traten die Diäten tatsächlich an. Allen Teilnehmern wurde empfohlen, mindestens drei Mal pro Woche für 30 Minuten (sportlich) aktiv zu werden, täglich Multivitamine einzunehmen und sechs bis acht Gläser Flüssigkeit zu trinken sowie den Alkohol- und Koffeinkonsum zu minimieren. Weder die Teilnehmer, noch das Studienpersonal wurden verblindet. Die Dauer der Intervention betrug 48 Wochen. (Yancy et al., 2010)

Für die Teilnehmer der LCKD wurde der Konsum von maximal 20 g Kohlenhydraten pro Tag festgesetzt. Neben dem uneingeschränkten Konsum von Fleisch und Eiern, durften täglich 112 g Hartkäse, 0,48 L kohlenhydratärmer Gemüsesorten (z. B. Blattsalat) und 0,24 L kohlenhydratmoderer Gemüsesorten (z. B. Brokkoli, Spargel) verspeist werden. Die Kalorienzufuhr wurde nicht beschränkt. Bei aufkommenden Gelüsten durfte auf 25 g Kohlenhydrate pro Tag erhöht werden. (Yancy et al., 2010)

Die Ergebnismessungen unterlagen der Durchführung von geschultem Forschungspersonal. Das Körpergewicht wurde bei jedem Besuch zur gleichen Tageszeit mit der gleichen kalibrierten Waage gemessen, wobei die Teilnehmer leichte Kleidung und keine Schuhe trugen. Die Einhaltung der Diät ermittelte man anhand von viertägigen Lebensmittelaufzeichnungen (einschließlich zwei Wochenendtagen) zu Studienbeginn und in den Wochen zwei, zwölf, 24, 36 und 48. Darüber hinaus fanden Gruppentreffen statt, die in der Studie jedoch nicht näher beschrieben werden. (Yancy et al., 2010)

## Studie 2

Titel: „Greater Loss of Central Adiposity from Low-Carbohydrate versus Low-Fat Diet in Middle-Aged Adults with Overweight and Obesity“

Autoren: Garr Barry, Valene; Stewart, Mariah; Soleymani, Taraneh; Desmond, Renee A.; Goss, Amy M.; Gower, Barbara A.

Zeitschrift und Jahr: Nutrients (2021)

Das Ziel dieser Studie war die Überprüfung, mittels welchen Diät-Konzepts Erwachsene mittleren Alters mit Übergewicht oder Adipositas mehr zentrales Fett verlieren würden. Verglichen wurde eine kohlenhydratreduzierte, fettreiche Diät (low-

carbohydrate high-fat (LCHF)) mit einer fettreduzierten Diät (low-fat (LF)). (Garr Barry et al., 2021)

Im Zeitraum von Mai 2014 bis Januar 2017 wurden Personen aus einer medizinisch betreuten Gewichtsverlustklinik der Universität von Alabama, Birmingham, rekrutiert. Darüber hinaus wurden Personen u. a. per Flyer, Zeitungs- und Internet-Werbeanzeigen angesprochen. Die Einschlusskriterien umfassten einen BMI von über 25 kg/m<sup>2</sup>, eine Gewichtsstabilität in den vorangegangenen zwölf Monaten (weniger als 4,5 kg Zu-/ Abnahme) und keine aktive Beteiligung in einem weiteren Gewichtsverlustprogramm. Typ-2-Diabetiker waren ebenso zur Teilnahme berechtigt, wenn keine Insulinabhängigkeit vorlag. Zu den Ausschlusskriterien gehörten ein Alter von über 75 Jahren, ein BMI von über 50 kg/m<sup>2</sup>, gegenwärtiges Rauchen, das Vorliegen einer Schwangerschaft oder gegenwärtiges Stillen. 80 Personen erfüllten die Einschlusskriterien, stimmten einer Teilnahme zu und wählten demnach eine der zwei möglichen Diät-Gruppen eigenständig aus (LCHF: n = 48; LF: n = 32). Um die passendere Diät herauszufinden, wurden vor dem Versuch Gespräche mit allen Teilnehmern und einem registrierten Ernährungsberater durchgeführt. In Absprache mit ärztlichem Personal, spezialisiert auf Gewichtsverlust, fand die Auswahl der Diäten statt. Die Dauer der Intervention betrug 15 Wochen. (Garr Barry et al., 2021)

Die LCHF-Diät setzte eine Makronährstoffverteilung von 5%:30%:65% (Kohlenhydrate:Proteine:Fette) des Gesamtenergiebedarfs voraus und förderte den Konsum von einfach und mehrfach ungesättigten Fettsäuren. Den Teilnehmern war vorgegeben, drei Mahlzeiten sowie bis zu zwei Snacks pro Tag zu essen. Darüber hinaus wurde der Konsum von maximal 20 g Kohlenhydraten pro Tag, davon 12 – 15 g aus Gemüse, festgesetzt. Neben rund 115 g Protein je Mahlzeit, wurde der Verzehr von täglich 115 g Milchprodukten, ca. 250 g gekochtem, nicht stärkehaltigem Gemüse sowie 500 g Blattgemüse empfohlen. Bei zusätzlichem Energiebedarf sollte auf gesunde Fette, wie bspw. Avocado, Oliven oder Olivenöl zurückgegriffen werden. Nach acht Wochen Diät durften die Teilnehmer auf 30 g Kohlenhydrate pro Tag erhöhen und Nüsse, Nussmus sowie Beeren in ihre Diät einbinden. Die Kalorienzufuhr wurde nicht beschränkt. (Garr Barry et al., 2021)

Um den Teilnehmern bei der Einhaltung der Diät zu helfen, stellte das Studienpersonal Richtlinien zur Ernährungsform, beispielhafte Ernährungs-Pläne sowie Rezepte zur Verfügung bereit. Obendrein wurden wöchentliche Gruppen-Sitzungen angeboten, in

welchen die Teilnehmer Themen, wie schnelles Kochen, achtsames Essen sowie gesunde Austausch- und Ersatzprodukte diskutieren konnten. Die Ergebnismessungen wurden vor Beginn der Intervention und nach 15 Wochen durchgeführt. Sie umfassten u. a. die Körperzusammensetzung sowie Standardwerte, wie das Körpergewicht. Die Kontrolle über die Einhaltung der Diät erfolgte anhand von dreitägigen Lebensmittelaufzeichnungen und durch die Messung des Körpergewichts in den Wochen zwei, vier, acht, zwölf und 15. (Garr Barry et al., 2021)

### Studie 3

Titel: „A Randomized Trial of a Low-Carbohydrate Diet for Obesity“

Autoren: Foster, Gary D.; Wyatt, Holly R.; Hill, James O.; McGuckin, Brian G.; Brill, Carrie; Mohammed, B. Selma; Szapary, Philippe O.; Rader, Daniel J.; Edman, Joel S.; Klein, Samuel

Zeitschrift und Jahr: The New England Journal of Medicine (2003)

Der Hintergrund dieser Studie ist der Beweis der Wirksamkeit der populär gewordenen kohlenhydratreduzierten, protein- und fettreichen Atkins-Diät. Hierfür wurde das eben genannte Diät-Konzept mit einer konventionellen kalorien- und fettreduzierten Diät mit hohem Kohlenhydrat-Anteil verglichen. (Foster et al., 2003)

Es wurde eine multizentrische, randomisierte, kontrollierte Studie mit 63 adipösen Personen durchgeführt. Alle Teilnehmer wurden umfassend medizinisch untersucht und unterlagen einer routinemäßigen Blutuntersuchung. Zu den Ausschlusskriterien zählten klinisch signifikante Krankheiten, einschließlich Typ-2-Diabetes, die Einnahme von lipidsenkenden oder das Körpergewicht beeinflussenden Medikamenten sowie das Vorliegen einer Schwangerschaft oder gegenwärtiges Stillen. Die Teilnehmer wurden einer der zwei möglichen Diät-Gruppen randomisiert zugeordnet. Alle Probanden erhielten die Anweisung, täglich ein Multivitaminpräparat einzunehmen und sich nach drei, sechs und zwölf Monaten mit einem registrierten Ernährungsberater für 15 – 30 Minuten zu unterhalten. Die Dauer der Intervention betrug ein Jahr. (Foster et al., 2003)

Die Teilnehmer der kohlenhydratreduzierten, protein- und fettreichen Diät, trafen sich vor Beginn des Programms individuell mit einem registrierten Ernährungsberater, um

die zentralen Merkmale der Diät zu erfassen. Diese beinhalteten eine begrenzte Kohlenhydrataufnahme, ohne den Verzehr von Fett und Protein einzuschränken. In den ersten zwei Wochen der Diät wurde der Konsum von Kohlenhydraten auf 20 g pro Tag beschränkt. In den Folgewochen war eine allmähliche Steigerung erlaubt, bis die Teilnehmer ein stabiles und das gewünschte Gewicht erreichten. Jede Person bekam eine Kopie des Buchs „Dr. Atkins‘ New Diet Revolution“ ausgehändigt, mit der Anweisung, es zu lesen und dem Diät-Programm zu folgen. (Foster et al., 2003)

Das Körpergewicht wurde mittels einer kalibrierten Waage in den Wochen zwei, vier, acht, zwölf, 16, 20, 26, 34, 42 und 52 gemessen, wobei die Teilnehmer leichte Kleidung und keine Schuhe trugen. (Foster et al., 2003)

## Studie 4

Titel: „Weight loss on low-fat vs. low-carbohydrate diets by insulin resistance status among overweight adults and adults with obesity: A randomized pilot trial“

Autoren: Gardner, Christopher D.; Offringa, Lisa C.; Hartle, Jennifer C.; Kapphahn, Kris; Cherin, Rise

Zeitschrift und Jahr: Obesity (2016)

Die Studie hatte zum Ziel, zwei verschiedene Diät-Konzepte bzgl. einer Gewichtsabnahme zu testen. Im Rahmen des Versuchs wurde eine kohlenhydratreduzierte Diät (low-carbohydrate (LC)) mit einer fettreduzierten Diät (low-fat (LF)) verglichen. Darüber hinaus stand ebenso die Gesamtqualität der beiden Diät-Formen im Vordergrund. (Gardner et al., 2016)

Im Zeitraum von Februar – April 2012 wurden 528 potentielle Teilnehmer hauptsächlich durch Medienwerbung aus der lokalen Gemeinschaft rekrutiert. Die Einschlusskriterien umfassten prämenopausale Frauen und Männer im Alter von 18 – 50 Jahren, einen BMI von 28 – 40 kg/m<sup>2</sup>, ein stabiles Körpergewicht der letzten zwei Monate sowie eine stabile bzw. unauffällige Medikamenteneinnahme der vorangegangenen drei Monate. Zu den Ausschlusskriterien gehörten u. a. eine Herz-, Leber- oder Nierenerkrankung, die Einnahme von gewichtsbeeinflussenden Medikamenten, das Vorliegen einer Schwangerschaft oder gegenwärtiges Rauchen. Alle Angaben sind Selbstangaben der potentiellen Teilnehmer. 61 Personen erfüllten

die Einschlusskriterien, stimmten einer Teilnahme zu und wurden den Diät-Gruppen randomisiert zugeordnet. Allen Teilnehmern wurde empfohlen, (sportlich) aktiv zu bleiben oder mit Bewegungseinheiten zu beginnen; Teilnehmer, die bereits regelmäßig trainierten, wurden ermutigt, ihr Pensum zu erhöhen. Alle Teilnehmer erhielten einen Schrittzähler. Das Studienpersonal wurde für die Behandlungszuweisung der Teilnehmer verblindet. Die Dauer der Intervention betrug sechs Monate. (Gardner et al., 2016)

Die LC-Diät zeigte vier zentrale Komponenten auf. Zu Beginn bestand die Frage "Wie tief kannst du gehen?" (Limbo). Die Teilnehmer wurden angewiesen, ihren Kohlenhydrat-Konsum auf 20 g pro Tag zu reduzieren. Innerhalb der ersten acht Wochen sollte somit die niedrigste Kohlenhydrataufnahme erreicht werden. Die zweite Stufe (Titrate) bestand darin, der Diät Kohlenhydrate in Schritten von 5 g pro Tag (von 20 g auf 25 g täglich) hinzuzufügen und dies für bis zu vier Wochen zu halten. Daraufhin konnten weitere 5 g Kohlenhydrate täglich ergänzt werden. Im Rahmen der dritten Stufe der Diät galt es für die Teilnehmer, das niedrigste Kohlenhydrat-Niveau, welches langfristig und mit Wohlbefinden aufrechterhalten werden konnte, herauszufinden. Anschließend lag der Fokus darauf, qualitativ hochwertige Lebensmittel mit hoher Nährstoffdichte vorrangig auszuwählen und zu konsumieren (Stufe 4). Die Teilnehmer konnten sich an Konzepten, wie „minimal verarbeitet“, „saisonal“ oder „echte Lebensmittel“ etc. orientieren. Weiterhin bekamen sie die Anweisung, möglichst ausschließlich Wasser zu trinken, den Gemüse-Anteil zu maximieren und auf Zucker, stark verarbeitete Produkte sowie Transfette zu verzichten. Des Weiteren wurden die Probanden gebeten, täglich eine halbe Avocado sowie weitere pflanzenbasierte Fette, u. a. aus Samen, Oliven und Nussmus zu verzehren. Es erfolgte keine Beschränkung der Kalorienzufuhr. (Gardner et al., 2016)

Die Intervention war ein klassenbasiertes Bildungsprogramm, das von einem einzelnen Gesundheitspädagogen geleitet wurde. In 14 einstündigen Kursen über einen Zeitraum von sechs Monaten hinweg, standen neben der Erarbeitung von Strategien zur Senkung des Kohlenhydrat-Anteils auch Themen, wie bspw. achtsames Essen, adäquater Schlaf, Selbstakzeptanz und Zuckerabhängigkeit im Mittelpunkt. Die Ergebnismessungen fanden jeweils nach drei und nach sechs Monaten statt. Größe, Körpergewicht und Taillenumfang wurden so präzise, wie möglich gemessen. Für Informationen über die Einhaltung der Diät und der physischen Aktivität führte man zu

den jeweiligen Zeitpunkten je drei, für die Teilnehmer unangekündigte Telefon-Interviews durch. Sie hatten 24 Stunden Zeit, um den möglicherweise verpassten Anruf zu entgegnen. Die Interviews fanden an zwei Wochentagen und an einem Wochenendtag in einem Zeitraum von zwei Wochen statt. (Gardner et al., 2016)

## Studie 5

Titel: „Long-term effects of weight loss with a very low carbohydrate and low fat diet on vascular function in overweight and obese patients“

Autoren: Wycherley, T. P.; Brinkworth, G. D.; Keogh, J. B.; Noakes, M.; Buckley, J. D.; Clifton, P. M.

Zeitschrift und Jahr: Journal of internal medicine (2010)

Der Hintergrund dieser Studie war der Vergleich zweier Diät-Konzepte und möglicherweise damit verbundene Auswirkungen auf das Körpergewicht. Verglichen wurden eine kalorien- und kohlenhydratreduzierte Diät (LC) mit einer isokalorischen fettarmen Diät (LF). (Wycherley et al., 2010)

Es wurden 122 abdominal adipöse Personen mit einem Alter von 24 – 64 Jahren und einem BMI von 26 – 43 kg/m<sup>2</sup> rekrutiert. Als Einschlusskriterium musste mindestens ein zusätzlicher Risikofaktor für das metabolische Syndrom vorliegen. Zu den Ausschlusskriterien zählten u. a. eine vorangegangene Leber- oder Herzerkrankung, gegenwärtiges Rauchen, das Vorliegen einer Schwangerschaft oder Diabetes. 107 Personen erfüllten die Einschlusskriterien, stimmten einer Teilnahme zu und wurden demnach einer der zwei möglichen Diät-Gruppen randomisiert zugeordnet. Die Dauer der Intervention betrug 52 Wochen. (Wycherley et al., 2010)

Die LC-Diät setzte eine Makronährstoffverteilung von 4%:35%:61% (Kohlenhydrate:Proteine:Fette) des Gesamtenergiebedarfs voraus. Darüber hinaus wurden die Teilnehmer angewiesen, die ersten acht Wochen nicht mehr als 20 g Kohlenhydrate pro Tag zu konsumieren. Optional konnte für die verbleibenden zehn Monate der Diät auf bis zu 40 g Kohlenhydrate täglich erhöht werden. Die Diät beinhaltete eine geringe Kalorienrestriktion, welche sich auf rund 1.500 kcal für Frauen und 1.750 kcal für Männer beläuft. (Wycherley et al., 2010)

Um die Einhaltung der Diät zu kontrollieren, besuchten die Teilnehmer einen qualifizierten Ernährungsberater in einer Klinik. Während der Konsultationen, welche vierzehntägig für die ersten acht Wochen und monatlich im Zeitraum danach stattfanden, erhielten die Teilnehmer einerseits Ernährungsberatungen und konnten andererseits ihre Fortschritte aufzeigen. Die Diäten wurden anhand bestimmter Lebensmittelmengen so strukturiert, dass der richtige Makronährstoff- und Energiebedarf erreicht werden konnte. Weiterhin wurden die Probanden dazu angehalten, ihre täglich verzehrten Lebensmittel und Mahlzeiten in einer Lebensmittelaufzeichnung zu notieren. Um die ganzheitliche Ernährung besser analysieren zu können, wurden in je zwei Wochen drei zufällige Tage (zwei Wochentage und ein Wochenendtag) und deren Lebensmittelaufzeichnungen ausgewählt und bewertet; dies wurde entsprechend 26-mal in 52 Wochen durchgeführt und repräsentiert die Diät ernährungsseitig. (Wycherley et al., 2010)

Die Ergebnismessung wurde ausschließlich in Woche 52 durchgeführt. Die Teilnehmer wurden gebeten, 24 Stunden vor dem Messen des Körpergewichts zu fasten und nicht zu trainieren. Zur Minimierung von Bias, wurde das Forschungspersonal, welches die Ergebnisbewertungen durchführte (Datensammler und Datenanalysten), für die Behandlungszuweisung verblindet. (Wycherley et al., 2010)

### Inhalte der Vergleichs-Diäten

Alle Vergleichs-Diäten der fünf vorab vorgestellten Studien legten den Fokus auf eine kohlenhydratreiche und fettarme Ernährung; damit liegt ein direkter Kontrast zu den ketogenen Diäten vor.

Studie 1 beschränkte den gesamten Fett-Anteil auf unter 30 Prozent des täglichen Energiebedarfs. Dabei passte sich zudem, individuell für jeden Teilnehmer, die tägliche Kalorienaufnahme an. Diese sollte ca. 500 – 1000 kcal unter dem zu Beginn errechneten Kalorienbedarf für einen Gewichtserhalt liegen. Monatlich stand ausreichend Orlistat zur Verfügung. Den Teilnehmern wurde empfohlen, mindestens drei Mal pro Woche für 30 Minuten (sportlich) aktiv zu werden, täglich Multivitamine einzunehmen und sechs bis acht Gläser Flüssigkeit zu trinken sowie den Alkohol- und Kaffeekonsum zu minimieren. (Yancy et al., 2010)

Studie 2 setzte eine Makronährstoffverteilung von 63%:13-23%:10-25% (Kohlenhydrate:Proteine:Fette) des Gesamtenergiebedarfs voraus. Der Energiebedarf wurde zudem auf 1200 – 1600 kcal pro Tag, basierend auf einer individuellen 500 kcal-Reduktion, in Abhängigkeit zur Ausgangs-Energieaufnahme, begrenzt. Die Diät betonte den Verzehr von Lebensmitteln mit niedriger Energiedichte, eine angemessene Portionsgröße sowie die Verwendung fettarmer Produkte, um den Energiebedarf nicht zu übersteigen. Die LF-Richtlinien und die entsprechenden Mahlzeitenpläne empfehlen, Gemüse statt Obst und Obst statt Stärke zu wählen sowie Milchprodukte häufiger als Fleisch- oder Proteinquellen und Fleisch bzw. Protein häufiger als Fett zu konsumieren. Obendrein wurden wöchentliche Gruppen-Sitzungen angeboten, in welchen Themen, wie schnelles Kochen, achtsames Essen sowie gesunde Austausch- und Ersatzprodukte diskutiert wurden. (Garr Barry et al., 2021)

Studie 3 setzte eine Makronährstoffverteilung von 60%:25%:15% (Kohlenhydrate:Fette:Proteine) des Gesamtenergiebedarfs voraus. Darüber hinaus wurde der Energiebedarf auf 1200 – 1500 kcal für Frauen und auf 1500 – 1800 kcal für Männer beschränkt. Die Teilnehmer erhielten den Auftrag, Kalorien zu zählen und bekamen die Möglichkeit, das „LEARN Programm for Weight Management“ zu lesen. Weiterhin wurde ihnen angewiesen, täglich ein Multivitaminpräparat einzunehmen und sich nach drei, sechs und zwölf Monaten mit einem registrierten Ernährungsberater für 15 – 30 Minuten zu unterhalten. (Foster et al., 2003)

Studie 4 folgte dem Diät-Konzept mit vier verschiedenen Stufen, wobei in den ersten acht Wochen der Fett-Anteil auf 20 g pro Tag beschränkt wurde (Limbo); in Stufe zwei konnte allmählich um 5 g Fett pro Tag erhöht werden (Titrate). Die Teilnehmer konnten sich an Konzepten, wie „minimal verarbeitet“, „saisonal“ oder „echte Lebensmittel“ etc. orientieren. Weiterhin bekamen sie die Anweisung, möglichst ausschließlich Wasser zu trinken, den Gemüse-Anteil zu maximieren und auf Zucker, stark verarbeitete Produkte sowie Transfette zu verzichten. Es fanden 14 einstündige Kurse über einen Zeitraum von sechs Monaten hinweg statt, in welchen u. a. Themen, wie achtsames Essen, adäquater Schlaf, Selbstakzeptanz und Zuckerabhängigkeit behandelt wurden. (Gardner et al., 2016)

Studie 5 setzte eine Makronährstoffverteilung von 46%:24%:30% (Kohlenhydrate:Proteine:Fette) des Gesamtenergiebedarfs voraus. Der Anteil von gesättigten Fettsäuren sollte hierbei täglich und für die gesamte Dauer der Intervention

unter zehn Gramm liegen. Die Diät beinhaltete eine geringe Kalorienrestriktion, welche sich auf rund 1.500 kcal für Frauen und 1.750 kcal für Männer beläuft. Um die Einhaltung der Diät zu kontrollieren, besuchten die Teilnehmer einen qualifizierten Ernährungsberater in einer Klinik. Während der Konsultationen, welche vierzehntägig für die ersten acht Wochen und monatlich im Zeitraum danach stattfanden, erhielten die Teilnehmer einerseits Ernährungsberatungen und konnten andererseits ihre Fortschritte aufzeigen. (Wycherley et al., 2010)

## 5.2 Studienergebnisse

Die Auswertung der Studienergebnisse wird sich insbesondere auf den Gewichtsverlust der Studienteilnehmer fokussieren. Neben diesem standen weitere Aspekte, wie Veränderungen des Blutdrucks, des Serumlipid-Status oder des Lipoprotein-Spiegels im Mittelpunkt, worauf jedoch nicht genauer, aufgrund der Differenz zur Fragestellung, eingegangen wird.

Die Angaben zu statistischer Signifikanz beziehen sich in allen Studien auf ein Konfidenzintervall von 95 % ( $p < 0,05$ ) und werden daher im Nachfolgenden nicht erneut erwähnt.

Die Teilnehmer beider Gruppen der Studie 1 konnten einen statistisch signifikanten Gewichtsverlust erzielen. Den Probanden gelang nach Woche 48 eine durchschnittliche Gewichtsreduktion von 11,37 kg (9,48 %) in der LCKD und von 9,62 kg (8,53 %) in der O + LFD. Ein signifikanter Unterschied zwischen beiden Gruppen blieb jedoch aus. Der Taillen-Umfang nahm in beiden Gruppen ebenso in ähnlichem Ausmaß ab. Personen, die zu 80 Prozent oder häufiger an den Gruppen-Treffen teilnahmen, verloren, unabhängig der Diät-Form, wesentlich mehr Gewicht (- 14,9 % LCKD; - 13,9 % O + LFD). (Yancy et al., 2010)

Die Gesamtabschlussrate der Studie 2 betrug 63 Prozent ( $n = 50$ ) und unterschied sich statistisch nicht zwischen den Gruppen: 67 Prozent ( $n = 32$ ) in der LCHF-Gruppe und 56 Prozent ( $n = 18$ ) in der LF-Gruppe. Die Teilnehmer beider Gruppen konnten eine statistisch signifikante Gewichts- und Körperfettreduktion verzeichnen. Den Probanden gelang nach Woche 15 eine durchschnittliche Gewichtsreduktion von 6,1 kg (5,4 kg Fett) in der LCHF-Gruppe und von 3,1 kg (3,0 kg Fett) in der LF-Gruppe.

Ein signifikanter Unterschied zwischen beiden Gruppen blieb jedoch aus. (Garr Barry et al., 2021)

Der prozentuale Anteil der Personen, welche die Teilnahme an Studie 3 vorzeitig abbrachen, war in der Gruppe der konventionellen Diät höher, als in der Vergleichs-Gruppe; der Unterschied ist jedoch nicht statistisch signifikant. Die Teilnehmer der kohlenhydratreduzierten Diät verloren nach drei und nach sechs Monaten signifikant mehr Gewicht, als die Teilnehmer der konventionellen Diät. Nach zwölf Monaten konnte kein signifikanter Unterschied zwischen den Gruppen festgestellt werden. Den Probanden gelang nach zwölf Monaten eine durchschnittliche Gewichtsreduktion von 7,3 % mit der kohlenhydratreduzierten Diät und von 4,5 % mit der konventionellen Diät. (Foster et al., 2003)

Von 61 Teilnehmern der Studie 4, führten 49 Personen (80 %) die Intervention bis zum Abschluss durch. Die durchschnittliche Beteiligung an den Kursen lag bei 81 Prozent in der LF-Gruppe und bei 85 Prozent in der LC-Gruppe. Den Probanden gelang nach sechs Monaten eine durchschnittliche Gewichtsreduktion von 9,6 kg bzw. 8,6 kg in der LC-Gruppe und von 7,4 kg bzw. 10,4 kg in der LF-Gruppe. Hierbei wurde zusätzlich zwischen insulinresistenten und insulinsensitiven Personen unterschieden. Ein signifikanter Unterschied zwischen beiden Gruppen blieb jedoch aus. (Gardner et al., 2016)

Den Probanden der Studie 5 gelang nach Woche 52 eine durchschnittliche Gewichtsreduktion von 14,9 kg in der LC-Gruppe und von 11,5 kg in der LF-Gruppe. Der BMI nahm durchschnittlich in den Gruppen wie folgt ab: - 5,3 kg/m<sup>2</sup> in der LC-Gruppe, - 3,9 kg/m<sup>2</sup> in der LF-Gruppe. Ein signifikanter Unterschied blieb sowohl im Rahmen der Gewichts-, als auch BMI-Reduktion zwischen beiden Gruppen aus. (Wycherley et al., 2010)

## 6 Diskussion

Das Ziel der vorliegenden Arbeit lag in der Entwicklung einer Übersicht aller relevanten wissenschaftlichen Literaturquellen bzw. Studien zum Thema Gewichtsreduktion bei Adipositas und Präadipositas im Erwachsenenalter im Rahmen einer ketogenen Diät, anhand derer die Wirksamkeit Letzterer geprüft werden sollte. In diesem Teil der Arbeit erfolgt die Bewertung der erschlossenen Ergebnisse, gefolgt von einer methodenkritischen Auseinandersetzung.

### 6.1 Ergebnisbewertung

Den Teilnehmern aller Studien gelang es, im Rahmen der kohlenhydratreduzierten Diät ihr Gewicht zu reduzieren. Anhand dessen kann die Diät als eine funktionierende Alternative zur konventionellen fettarmen Diät angesehen werden. Dennoch darf die ketogene Ernährungsweise nicht als effektiver bezeichnet werden, da der signifikante Unterschied hinsichtlich des Gewichtsverlustes in allen Studien, unabhängig von der Dauer der Interventionen, ausblieb. Lediglich Studie 3 berichtete von einem signifikant höheren Gewichtsverlust mit der ketogenen Diät nach jeweils drei und sechs Monaten. Dies könnte darauf zurückzuführen sein, dass die Probanden nicht über die Merkmale der Ernährungsweise informiert worden sind, sondern sich alle einzelnen Schritte und Details der Diät mit Atkins' Buch aneigneten und jederzeit nachschlagen konnten. Weiterhin wäre der ähnlich hohe Gewichtsverlust mit den fettarmen Diäten mit den zumeist vorgegebenen Kalorienbegrenzungen begründbar. Eine Abnahme lässt sich hiermit genau kontrollieren. Eine effektive Unterstützung zur Gewichtsreduzierung stellt eine Verhaltenstherapie dar. Wie Studie 1 zeigt, verloren Probanden, welche regelmäßig an Gruppen-Sitzungen teilnahmen, zu 80 % mehr Gewicht – rund 15 % des Körpergewichts. Auch die Studien 2, 4 und 5 führten solche Gruppen-Sitzungen bzw. Konsultationen durch. Jedoch können über deren Effektivität keine Schlüsse gezogen werden. Bemerkenswert sind zudem die Ergebnisse der Studie 2, bei der keine Randomisierung der Probanden vorgenommen wurde. Trotz dessen erzielten sie einen ebenso hohen Gewichtsverlust, verglichen mit denen der anderen Studien, in einem jedoch kleineren Zeitraum (15 Wochen). Errechnet man den durchschnittlichen Gewichtsverlust der Studie 2 nach etwa 52 Wochen, so wäre dieser wohlmöglich höher als die Vergleichswerte der anderen Studien. Die nicht erfolgte

Randomisierung kann zum einen zu unerwünschten Effekten und vermehrten Störgrößen (Döring & Bortz, 2016), zum anderen jedoch auch zu einer besseren Einhaltung der Diät führen.

Weiterhin kam es zu verschiedenen Angaben innerhalb der Artikel, welche u. a. nicht interpretiert werden konnten: Studie 1 setzte ernährungsseitig den Verzehr von 0,48 L kohlenhydratärmer Gemüsesorten und 0,24 L kohlenhydratmoderer Gemüsesorten täglich voraus; die genannte Einheit konnte nicht zugeordnet werden und entfällt daher der Interpretation. Des Weiteren wurden die durchgeführten Gruppen-Sitzungen nicht näher beschrieben. Laut Studie 2 konsumierten die Teilnehmer drei Mal je 115 g Protein täglich – dies übersteigt jede Empfehlung und wird daher als nicht notwendig angesehen. In Studie 3 wurden zum einen keine Gruppen-Sitzungen durchgeführt und zum anderen nur drei 15 – 30-minütige Gespräche mit einem Ernährungsberater innerhalb der gesamten Intervention (zwölf Monate) angeboten. Dieser Umfang erscheint für die Dauer zu gering gewählt. Der zu selten gegebene Hinweis, ausreichend Gemüse in die Diät zu integrieren, wird ebenso negativ bewertet. Lediglich Studie 1 und 2 erwähnten den Konsum von Gemüse.

Dass die Diäten dennoch erfolgreich verlaufen sind, lässt sich mit dem Fakt, dass eine Gewichtsabnahme von fünf Prozent des Ausgangsgewichtes bereits in vielen Fällen einen Erfolg darstellt und zur Risikominderung von Folgeerkrankungen führt, belegen (Benecke & Vogel, 2003; Leitzmann et al., 2009). Bei einem durchschnittlichen Ausgangsgewicht von rund 100 – 120 kg der Teilnehmer erfüllte die Mehrheit diese Vorgabe.

Nicht erforscht werden konnte, ob der Gewichtsverlust mit einer ketogenen Diät langfristige Erfolge erzielen kann. Die maximale Dauer der Interventionen betrug zwölf Monate. Im Gegensatz dazu konnte durch Studie 1 bewiesen werden, dass aus einer unterstützenden Verhaltenstherapie, eine bis zu durchschnittlich 15-prozentig höhere Gewichtsabnahme resultieren kann.

## 6.2 Methodenkritik

Das methodische Vorgehen dieser Arbeit ist positiv verlaufen und kann als gelungen bezeichnet werden. Mithilfe der Suchstrings konnten Studien ausfindig gemacht werden, deren Ergebnisse letztendlich die Fragestellung der vorliegenden Arbeit beantworteten. Nichtsdestotrotz führten einzelne Faktoren zu einer nicht einwandfreien Methodik. Zum einen konnte durch die Sprache einzelner Studien nicht sichergestellt werden, alle relevanten Artikel einzubeziehen. Da das Thema nicht nur auf Bundesebene angesetzt wurde, wäre der Einbezug relevanter Studien aller Staaten optimal gewesen. Das Verständnis war jedoch auf deutsch- und englischsprachig limitiert. Zum anderen könnten einzelne Datenbanken nach der abgeschlossenen Recherche aktualisiert worden sein, wodurch neue Studien nicht mehr einbezogen werden konnten. Nicht zuletzt können Fehler aus der fehlenden Erfahrung mit Datenbankrecherchen und deren Individualität resultieren.

## 7 Fazit

Die vorliegende Arbeit hat sich dem bestehenden Problem der hohen Adipositas-Prävalenz in Deutschland sowie weltweit und der damit verbundenen Todesfälle sowie Kosten im Gesundheitswesen angenommen und eine mögliche Therapie-Strategie untersucht. Im Mittelpunkt dieser stand, abseits der Empfehlungen der DGE, eine kohlenhydratreduzierte, protein- und fettreiche Kost. Diese Form der Diät könnte als Alternative zur konventionellen Diät für jene Personen, deren Abnehm-Versuche bislang ohne Erfolg blieben, gesehen werden. Die Wirksamkeit der sogenannten ketogenen Ernährungsform wurde anhand einer systematischen Literaturrecherche untersucht. Es konnten fünf Studien ausfindig gemacht werden, welche eine Gewichtsreduktion in Abhängigkeit von der kohlenhydratreduzierten Ernährung erforschten. Die Ergebnisse zeigten, dass die besagte Diät nicht effektiver, jedoch mindestens genau so wirksam, wie eine konventionelle Diät ist. Damit vergrößert sich das Spektrum der anwendbaren Möglichkeiten im Rahmen einer Adipositas-Therapie.

Zukünftig muss zu den Themen Übergewicht und Fettleibigkeit mehr Aufklärungsarbeit stattfinden. Erwachsene, d. h. auch Eltern, sind stark von Adipositas betroffen und wirken als Vorbildfunktion für Kinder und Heranwachsende. Wenn die Prävalenz stagniert oder weiterhin ansteigt, wird auch das Risiko, welches bereits jetzt auf den Jüngeren lastet, immer höher.

## VI Literaturverzeichnis

- Abernathy, R. P. & Black, D. R. (1996). Healthy body weights: an alternative perspective. *The American Journal of Clinical Nutrition*, 63(3), 448–451.  
<https://doi.org/10.1093/ajcn/63.3.448>
- Benecke, A. & Vogel, H. (2003). *Übergewicht und Adipositas. Gesundheitsberichterstattung des Bundes: Bd. 16.* Robert-Koch-Institut.
- Deutsche Adipositas-Gesellschaft e.V., Deutsche Diabetes Gesellschaft, Deutsche Gesellschaft für Ernährung e.V. & Deutsche Gesellschaft für Ernährungsmedizin e.V. (Hrsg.). (2014). *Interdisziplinäre Leitlinie der Qualität S3 zur „Prävention und Therapie der Adipositas“.*
- DGE (Hrsg.). (2017). *Vollwertig essen und trinken nach den 10 Regeln der DGE.*  
<https://www.dge.de/ernaehrungspraxis/vollwertige-ernaehrung/10-regeln-der-dge/>
- Döring, N. & Bortz, J. (2016). *Forschungsmethoden und Evaluation in den Sozial- und Humanwissenschaften* (5. Aufl.). Springer-Lehrbuch. Springer.
- Foster, G. D., Wyatt, H. R., Hill, J. O., McGuckin, B. G., Brill, C., Mohammed, B. S., Szapary, P. O., Rader, D. J., Edman, J. S. & Klein, S. (2003). A Randomized Trial of a Low-Carbohydrate Diet for Obesity. *The New England Journal of Medicine*, 348, 2082–2090.
- Gardner, C. D., Offringa, L. C., Hartle, J. C., Kapphahn, K. & Cherin, R. (2016). Weight loss on low-fat vs. low-carbohydrate diets by insulin resistance status among overweight adults and adults with obesity: A randomized pilot trial. *Obesity (Silver Spring, Md.)*, 24(1), 79–86. <https://doi.org/10.1002/oby.21331>
- Garr Barry, V., Stewart, M., Soleymani, T., Desmond, R. A., Goss, A. M. & Gower, B. A. (2021). Greater Loss of Central Adiposity from Low-Carbohydrate versus Low-Fat Diet in Middle-Aged Adults with Overweight and Obesity. *Nutrients*, 13(2). <https://doi.org/10.3390/nu13020475>
- Leitzmann, C., Müller, C., Michel, P., Brehme, U., Triebel, T., Hahn, A. & Laube, H. (2009). *Ernährung in Prävention und Therapie: Ein Lehrbuch* (3., vollst. überarb. und erw. Aufl.). Hippokrates-Verl.
- Nordhausen, T. & Hirt, J. (2020, 13. Oktober). *Manual zur Literaturrecherche in Fachdatenbanken.*

- Schienkiewitz A, Mensink GBM, Kuhnert R et al. (2017). Übergewicht und Adipositas bei Erwachsenen in Deutschland. *Journal of Health Monitoring*, 2(2), 21–28.  
<https://doi.org/10.17886/RKI-GBE-2017-025>
- Statista (Hrsg.). (2016a). *Direkte und indirekte Kosten für Adipositas (Fettleibigkeit) in Deutschland im Jahr 2015*.  
<https://de.statista.com/statistik/daten/studie/593247/umfrage/direkte-und-indirekte-kosten-fuer-adipositas-in-deutschland/>
- Statista (Hrsg.). (2016b). *Gesamtzahl und durch Adipositas bedingte Todesfälle bei ausgewählten Krankheiten 2014*.  
<https://de.statista.com/statistik/daten/studie/786707/umfrage/gesamtzahl-und-durch-adipositas-bedingte-todesfaelle-bei-ausgewaehlten-krankheiten/>
- WHO (Hrsg.). (2001). *Obesity: preventing and managing the global epidemic: report of a WHO consultation* (Nr. 894). Genf.  
<http://www.ncbi.nlm.nih.gov/pubmed/11234459>
- WHO (Hrsg.). (2021). *Obesity and overweight: Key facts*. <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>
- Wycherley, T. P., Brinkworth, G. D., Keogh, J. B., Noakes, M., Buckley, J. D. & Clifton, P. M. (2010). Long-term effects of weight loss with a very low carbohydrate and low fat diet on vascular function in overweight and obese patients. *Journal of internal medicine*, 267(5), 452–461. <https://doi.org/10.1111/j.1365-2796.2009.02174.x>
- Yancy, W. S., JR., Westman, E. C., McDuffie, J. R., Grambow, S. C., Jeffreys, A. S., Bolton, J., Chalecki, A. & Oddone, E. Z. (2010). A Randomized Trial of a Low-Carbohydrate Diet vs Orlistat Plus a Low-Fat Diet for Weight Loss. *JAMA Internal Medicine*, 170(2), 136–145. <https://jamanetwork.com/>
- Zok, C. (2012). Die Low-Carb-Diät – ein umstrittenes Ernährungskonzept. *Deutsche Medizinische Wochenschrift*, 137(36), 1730–1731.
- Zunft, H. J. (2011). Außenseiterdiäten. In P. Schauder, G. Ollenschläger & O. Adam (Hrsg.), *Ernährungsmedizin: Prävention und Therapie* (3. Aufl., S. 175–187). Elsevier Urban & Fischer.

## VII Eidestattliche Erklärung

„Hiermit versichere ich, dass ich die vorliegende Bachelorthesis selbstständig verfasst und keine anderen, als die angegebenen Quellen und Hilfsmittel verwendet habe. Alle Ausführungen, tabellarischen und bildlichen Darstellungen, die anderen Quellen wörtlich oder sinngemäß entnommen wurden, sind kenntlich gemacht. Die Arbeit in gleicher oder ähnlicher Fassung liegt als Prüfungsleistung noch keiner Prüfungsbehörde vor.“

Lena Heutehaus

Lena Heutehaus

Mülzen, 02.08.2021

## VIII Anhang: Artikel

# A Randomized Trial of a Low-Carbohydrate Diet vs Orlistat Plus a Low-Fat Diet for Weight Loss

William S. Yancy Jr, MD, MHS; Eric C. Westman, MD, MHS; Jennifer R. McDuffie, PhD, RD, MPH; Steven C. Grambow, PhD; Amy S. Jeffreys, MStat; Jamiyla Bolton, MS; Allison Chalecki, RD; Eugene Z. Oddone, MD, MHS

**Background:** Two potent weight loss therapies, a low-carbohydrate, ketogenic diet (LCKD) and orlistat therapy combined with a low-fat diet (O + LFD), are available to the public but, to our knowledge, have never been compared.

**Methods:** Overweight or obese outpatients ( $n=146$ ) from the Department of Veterans Affairs primary care clinics in Durham, North Carolina, were randomized to either LCKD instruction (initially, <20 g of carbohydrate daily) or orlistat therapy, 120 mg orally 3 times daily, plus low-fat diet instruction (<30% energy from fat, 500-1000 kcal/d deficit) delivered at group meetings over 48 weeks. Main outcome measures were body weight, blood pressure, fasting serum lipid, and glycemic parameters.

**Results:** The mean age was 52 years and mean body mass index was 39.3 (calculated as weight in kilograms divided by height in meters squared); 72% were men, 55% were black, and 32% had type 2 diabetes mellitus. Of the study participants, 57 of the LCKD group (79%) and 65 of the O + LFD group (88%) completed measurements

at 48 weeks. Weight loss was similar for the LCKD (expected mean change, -9.5%) and the O + LFD (-8.5%) ( $P=.60$  for comparison) groups. The LCKD had a more beneficial impact than O + LFD on systolic (-5.9 vs 1.5 mm Hg) and diastolic (-4.5 vs 0.4 mm Hg) blood pressures ( $P<.001$  for both comparisons). High-density lipoprotein cholesterol and triglyceride levels improved similarly within both groups. Low-density lipoprotein cholesterol levels improved within the O + LFD group only, whereas glucose, insulin, and hemoglobin A<sub>1c</sub> levels improved within the LCKD group only; comparisons between groups, however, were not statistically significant.

**Conclusion:** In a sample of medical outpatients, an LCKD led to similar improvements as O + LFD for weight, serum lipid, and glycemic parameters and was more effective for lowering blood pressure.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00108524

Arch Intern Med. 2010;170(2):136-145

**S**TUDIES COMPARING LOW-carbohydrate diets with reduced-calorie diets have shown that weight loss can be greater with a low-carbohydrate diet for durations of 6 months or less and similar or greater for durations up to 2 years.<sup>1-3</sup> Likewise, the 2 weight loss medications approved for long-term use,

## See also pages 121, 126, and 146

orlistat and sibutramine, when paired with a reduced-calorie diet, have proved more effective than diet alone.<sup>4</sup> Yet, neither of these medications has been compared with a low-carbohydrate diet. Now that orlistat is available without prescription, it is appropriate to compare it with other readily available, potent interventions such as the low-carbohydrate diet.

In addition, low-carbohydrate diets have been studied infrequently in patients with chronic illnesses.<sup>5-9</sup> With treatment guidelines beginning to include the low-carbohydrate diet as an option for such patients, it is important to study the diet's effect on chronic illnesses using rigorous research methods.<sup>10</sup> For example, patients taking medications that lower blood glucose level and blood pressure may respond differently to diets compared with healthy volunteers.<sup>5,8</sup> In this way, low-carbohydrate diets may be like weight loss medications in that medical monitoring is required and empirical experience is needed to inform practitioners. If a low-carbohydrate diet is at least comparable to a weight loss medication, it may be an attractive alternative to practitioners because it is simpler and less expensive than a diet plus medication combination therapy.

The purpose of this study was to examine body weight, metabolic, and ad-

**Author Affiliations:** Center for Health Services Research in Primary Care, Department of Veterans Affairs Medical Center, Durham, North Carolina (Drs Yancy, McDuffie, Grambow, and Oddone and Ms Jeffreys, Bolton, and Chalecki); and Departments of Medicine (Drs Yancy, Westman, and Oddone) and Biostatistics and Bioinformatics (Dr Grambow), Duke University Medical Center, Durham, North Carolina.

verse effects over 48 weeks in outpatients randomized to follow a low-carbohydrate, ketogenic diet (LCKD) or orlistat therapy plus a low-fat, reduced-calorie diet (O + LFD). Our hypothesis was that weight loss would be greater in participants following the LCKD.

## METHODS

### PARTICIPANTS

Participants were recruited from outpatient clinics affiliated with the Department of Veterans Affairs Medical Center in Durham, North Carolina, between April 2005 and October 2006. The inclusion criteria were age between 18 and 70 years and a body mass index (BMI) between 27 and 30 (calculated as weight in kilograms divided by height in meters squared) plus an obesity-related disease or a BMI of 30 or higher regardless of comorbidity.<sup>11</sup> Exclusion criteria included weight loss in the past month; pregnancy, breastfeeding, or lack of birth control; type 1 diabetes mellitus; unstable heart disease; dementia, unstable psychiatric illness, or substance abuse; blood pressure higher than 160/100 mm Hg; serum creatinine level higher than 1.5 mg/dL (to convert to micromoles per liter, multiply by 88.4) in men and higher than 1.3 mg/dL in women; liver transaminase level higher than 2 times the upper limit of normal, alkaline phosphatase level higher than 120 U/L (to convert to mikrokatal, multiply by 0.0167), or total bilirubin level higher than 1.6 mg/dL (to convert to micromoles per liter, multiply by 17.104); hemoglobin A<sub>1c</sub> level higher than 11% (to convert to a proportion of total hemoglobin, multiply by 0.01); and fasting serum triglyceride level higher than 600 mg/dL (to convert to millimoles per liter, multiply by 0.0113) or low-density lipoprotein cholesterol (LDL-C) level higher than 190 mg/dL (to convert to millimoles per liter, multiply by 0.0259). All participants provided written informed consent approved by the Durham VA Medical Center's institutional review board.

### RANDOMIZATION AND INTERVENTION

Eligible participants were allocated to the LCKD or O + LFD using a computer-generated randomization list kept exclusively by the study statisticians (S.C.G. and A.S.J.). Randomization was stratified by sex and presence of type 2 diabetes mellitus.

Both interventions included small group meetings (6 to 12 participants) at an outpatient clinic every 2 weeks for 24 weeks, then every 4 weeks for 24 weeks. Meetings lasted 1 to 2 hours and consisted of study measurements followed by group counseling led by a registered dietitian (A.C.), a research assistant (J.B.), and a physician (W.S.Y.). The counseling sessions followed a predetermined syllabus of topics (eg, nutrition label reading, eating out) that were parallel between the 2 interventions but specific to diet. All participants were advised to exercise on their own for 30 minutes at least 3 times per week, take a multivitamin daily, drink 6 to 8 glasses of fluids daily, and minimize consumption of caffeine and alcohol. Participants and study personnel were not blinded to treatment assignment.

### LOW-CARBOHYDRATE DIET

Participants were instructed to restrict carbohydrate intake initially to less than 20 g/d using pocket guides and handouts.<sup>12,13</sup> Participants could eat unlimited meat and eggs, 112 g of hard cheese, 0.48 L of low-carbohydrate vegetables (eg, leafy greens), and 0.24 L of moderate-carbohydrate vegetables (eg, broccoli, asparagus) daily; calorie intake was not

restricted. As participants approached their goal weight or if cravings threatened their adherence to the diet, they were advised to add approximately 5 g of carbohydrates to their daily intake each week until weight was maintained or cravings diminished.

### ORLISTAT PLUS LOW-FAT DIET

Participants were instructed to restrict intake of total fat (<30% of daily energy), saturated fat (<10% of daily energy), cholesterol (<300 mg daily), and calories using pocket guides, handouts, and individualized goals.<sup>13,14</sup> Recommended calorie intake was 500 to 1000 kcal below a participant's calculated weight maintenance intake.<sup>15</sup> In addition, a 30-day supply of orlistat (120 mg before meals 3 times a day) was provided monthly.

### OUTCOME MEASURES

Outcome measures were performed by trained research personnel. Body weight was measured using the same calibrated scale (Tanita Corp, Arlington Heights, Illinois) at each visit at the same time of day, with the participant wearing light clothing and no shoes. Blood pressure and pulse were measured twice at each visit in the nondominant arm using an automated digital cuff (Omron Corp, Vernon Hills, Illinois) after the participant was sitting for 5 minutes. The mean of the 2 readings was used in analyses. Similarly, waist circumference was measured twice at the skin surface at the level of the umbilicus using a nonelastic tape. Urinary ketones were measured at each visit from a fresh urine specimen.

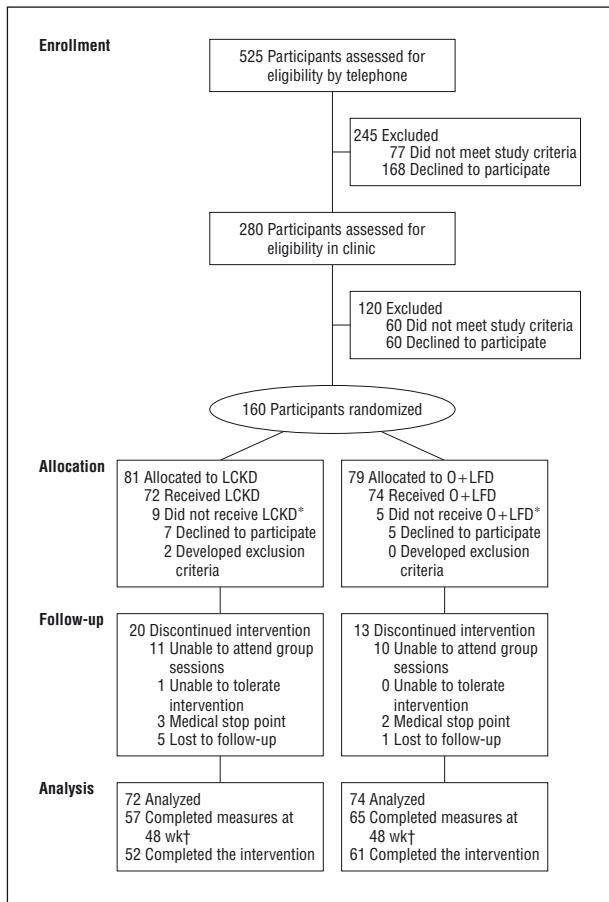
Diet adherence was measured using 4-day food records (including 2 weekend days) at baseline and weeks 2, 12, 24, 36, and 48. Participants were given verbal and written instructions regarding record completion. A registered dietitian (A.C. or J.R.M.) clarified ambiguous entries with the participant and input data using nutrition analysis software (ESHA Research, Salem, Oregon). Self-administered questionnaires were completed at group visits to assess medication changes, physical activity level, and adverse effects.<sup>16</sup>

Blood and urine samples were obtained after at least 8 hours of fasting at baseline and at weeks 2, 12, 24, 36, and 48. Processing and testing of samples were performed by the central laboratory of the medical center following standardized techniques; LDL-C level was calculated using the Friedewald equation.<sup>17</sup>

### STATISTICAL ANALYSIS

The primary outcome was percentage change in body weight. The sample size estimate, however, was based on the secondary outcome of mean change in LDL-C level because it has been considered a safety concern for the LCKD and has more stringent sample size requirements. Based on previous data, a 2-sided type 1 error rate of 0.05 and 80% power, we estimated that 140 participants (70 in each treatment group) were needed to detect a 9-mg/dL absolute difference between the 2 interventions in mean LDL-C level change from baseline to 48 weeks.<sup>18</sup> This estimate provided greater than 95% power to detect a 3% absolute difference between the interventions in mean percentage weight change. Sample size calculations assumed a 30% final dropout rate and accounted for clustering due to small meeting groups within each treatment condition.<sup>19</sup>

Baseline variables of the 2 interventions were compared using unpaired *t* tests for continuous variables and  $\chi^2$  tests for categorical variables. The primary analysis for outcomes was performed according to intention-to-treat principles; all participants who were randomized and had at least 1 outcome data



**Figure 1.** Participant flowchart. O + LFD indicates orlistat plus a low-fat, reduced-calorie diet; LCKD, low-carbohydrate, ketogenic diet. \*Participants who withdrew after randomization but before receiving the intervention were unaware of their allocation. †Nine participants (LCKD, n=5; O + LFD, n=4) returned for measurements at week 48 despite discontinuing the intervention.

measurement collected were included in analyses according to their randomized allocation.<sup>20</sup> Subjects who failed to attend their initial small group visit were unaware of their randomization assignment, did not have outcome data collected, and therefore, were not included in analyses. To compare categorical outcomes between groups, we used the Pearson  $\chi^2$  test. For continuous, longitudinal outcomes, we used linear mixed models to test hypotheses of treatment differences over time.<sup>21</sup> For body measurement and vital sign models, we used a random coefficient approach with time and treatment group included as fixed effects with linear, quadratic, or cubic time-by-treatment group interaction terms as appropriate<sup>22</sup>; random effects included intercept and slope terms (percentage change in weight did not include a random intercept term because, by definition, percentage change must be zero at baseline). In addition, the proportions of participants in each intervention who achieved levels of weight loss (<5%, 5% to <10%, 10% to <20%, and  $\geq 20\%$ ) were estimated using best linear unbiased predictors from the mixed model.<sup>23</sup> For serum tests (collected at 5 time points compared with 19 for body and vital sign measurements), we used a repeated-measures approach with the time-by-treatment group interaction as a categorical variable and an unstructured covariance to account for within-patient correlation over time. Longitudinal models used all available data, including data from participants who had missing observations and/or were lost to attrition; these models yield unbiased estimates of parameters when missing outcome data are assumed to be ignorable, ie,

the missing values may be related to either observed covariates or response variables but not related to the unobserved values.<sup>24</sup> Because there were no estimable small group effects, the presented analyses do not incorporate adjustment for clustering. Statistical analyses were performed using SAS software version 9.1 (SAS Institute Inc, Cary, North Carolina) and S-PLUS version 7 (Insightful Corp, Seattle, Washington).

## RESULTS

### PARTICIPANTS AND RETENTION

During recruitment, 525 volunteers were screened for eligibility by telephone, 280 were subsequently screened in the clinic, and 160 were randomized (**Figure 1**). Of those, 14 did not attend the first intervention visit and therefore did not learn of their intervention assignments nor have baseline outcome measurements. Baseline characteristics for the 146 participants who initiated the intervention are given in **Table 1**.

Of the 33 participants (LCKD, n=20; O + LFD, n=13) who discontinued the intervention, 9 (LCKD, n=5; O + LFD, n=4) agreed to return for week 48 measurements (Figure 1). Five participants were discontinued for safety reasons (LCKD, 2 for LDL-C elevations and 1 for a kidney stone; O + LFD, 1 for pregnancy and 1 for a kidney stone).

### DIET COMPOSITION AND ADHERENCE MEASURES

The 2 treatment groups had similar intakes of calories, macronutrients, and fiber at baseline (**Table 2**). Both groups had substantially reduced caloric intake over the course of the study compared with baseline. There were obvious differences in carbohydrate and fat intake between the groups during follow-up, as expected.

The presence of urinary ketones is a marker of adherence to the LCKD. The proportion of LCKD participants with urinary ketones present ( $\geq 5$  mg/dL [ $\geq 0.9$  mmol/L]) was 72% (50 of 69 participants) at 2 weeks and declined gradually to a low of 13% at 48 weeks. The proportion of O + LFD participants with urinary ketones remained below 15% with few exceptions.

We analyzed orlistat pill counts by calculating the percentage of pills taken over the course of the study excluding pill bottles never handed out (eg, participant did not attend a visit or discontinued the study) (15%) or never returned to be counted (15%). After analyzing those pill bottles returned, we found that a mean (SD) of 89% (15%) of pills were taken over the 48 weeks.

### BODY MEASUREMENTS

Over 48 weeks, weight loss was statistically significant and similar in the 2 groups: the expected mean change from baseline in the LCKD participants was  $-9.5\%$  (95% CI [confidence interval],  $-12.1$  to  $-6.9$ ) or  $-11.4$  kg (95% CI,  $-14.8$  to  $-7.9$ ) compared with  $-8.5\%$  (95% CI,  $-11.0$  to  $-6.1$ ) or  $-9.6$  kg (95% CI,  $-11.9$  to  $-7.3$ ) in the O + LFD participants (mean difference,  $-1.0\%$ ; 95% CI,  $-4.5$  to  $2.6$ ) (**Table 3**, **Figure 2**, and **Figure 3**). Waist circumference also decreased similarly in the 2 groups. The pro-

**Table 1. Baseline Participant Characteristics<sup>a</sup>**

Characteristic	LCKD			O + LFD			P Value for Between-Group Comparison of Enrollees <sup>b</sup>
	Enrollees (n=72)	Completers (n=57)	Noncompleters (n=15)	Enrollees (n=74)	Completers (n=65)	Noncompleters (n=9)	
Demographics							
Age, y	52.9 (10.2)	54.5 (9.7)	47.1 (10.2)	52.0 (9.2)	53.2 (8.9)	43.5 (5.7)	.57
Women, No. (%)	20 (28)	14 (25)	6 (40)	21 (28)	17 (26)	4 (44)	.94
Race or ethnicity, No. (%)							>.99
White	31 (43)	26 (46)	5 (33)	31 (42)	28 (43)	3 (33)	
African American	40 (56)	31 (54)	9 (60)	41 (55)	35 (54)	6 (67)	
College degree, No. (%)	33 (46)	28 (49)	5 (33)	33 (45)	29 (45)	4 (44)	.88
Risk factors, No. (%)							
Smokers	4 (6)	3 (5)	1 (7)	12 (16)	10 (15)	2 (22)	.04
Hypertension	44 (61)	38 (67)	6 (40)	54 (73)	50 (77)	4 (44)	.13
Hyperlipidemia	33 (46)	30 (53)	3 (20)	31 (42)	28 (43)	3 (33)	.63
Diabetes	22 (31)	17 (30)	5 (33)	24 (32)	23 (35)	1 (11)	.81
Framingham physical activity index, <sup>16</sup> score <sup>c</sup>	29.6 (4.0)	29.4 (3.7)	30.5 (5.0)	29.6 (4.3)	29.5 (4.3)	29.9 (4.7)	.96
Clinical measures							
Body weight, kg	123.1 (25.4)	124.0 (25.7)	119.9 (24.5)	117.4 (26.0)	119.0 (26.8)	105.4 (16.3)	.18
BMI	39.9 (6.9)	39.5 (6.9)	41.1 (7.0)	38.8 (7.0)	39.3 (7.2)	34.9 (3.5)	.36
Waist circumference, cm	127.4 (16.9)	127.6 (17.2)	126.5 (16.5)	124.8 (17.4)	126.1 (17.5)	115.4 (14.6)	.37
Systolic blood pressure, mm Hg	135.0 (17.0)	135.1 (16.4)	134.5 (19.5)	128.2 (15.5)	128.8 (15.9)	124.4 (11.9)	.01
Diastolic blood pressure, mm Hg	89.6 (9.7)	89.4 (9.3)	90.3 (11.2)	85.0 (10.4)	84.6 (10.8)	87.9 (5.7)	.01
Blood tests							
Total cholesterol, mg/dL	181.5 (32.1)	182.5 (33.7)	177.8 (25.6)	185.0 (34.4)	184.0 (35.2)	191.6 (28.9)	.54
Triglycerides, mg/dL	142.2 (73.8)	151.9 (74.3)	105.2 (60.8)	139.1 (74.3)	136.4 (74.1)	158.4 (76.9)	.80
LDL-C, mg/dL <sup>c</sup>	115.6 (29.8)	115.5 (31.4)	116.0 (23.8)	118.1 (31.4)	117.5 (32.4)	123.0 (23.6)	.62
HDL-C, mg/dL	37.6 (8.1)	36.7 (8.1)	40.7 (7.9)	39.1 (12.1)	39.4 (12.5)	36.9 (8.3)	.40
Triglyceride/HDL-C ratio	4.1 (2.7)	4.5 (2.7)	2.9 (2.1)	4.0 (2.6)	3.9 (2.6)	4.7 (2.8)	.73
C-reactive protein, mg/L	0.6 (0.5)	0.6 (0.4)	0.8 (0.7)	0.8 (0.7)	0.8 (0.8)	0.6 (0.4)	.17
Hemoglobin A <sub>1c</sub> , %	6.3 (1.1)	6.2 (1.0)	6.7 (1.4)	6.4 (1.3)	6.4 (1.4)	5.9 (0.9)	.78

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; LCKD, low-carbohydrate, ketogenic diet; LDL-C, low-density lipoprotein cholesterol; O + LFD, orlistat plus a low-fat, reduced-calorie diet.

SI conversion factors: To convert cholesterol and triglycerides to millimoles per liter, multiply by 0.0259 and 0.0113, respectively; C-reactive protein to nanomoles per liter, multiply by 9.524; and hemoglobin A<sub>1c</sub> to a proportion of total hemoglobin, multiply by 0.01.

<sup>a</sup>Data are given as mean (SD) unless otherwise specified.

<sup>b</sup>Baseline variables of the enrollees in the 2 interventions were compared using *t* tests for continuous variables and  $\chi^2$  tests for categorical variables.

<sup>c</sup>One patient in the LCKD completer group was missing a measurement for LDL-C; 1 patient in the LCKD noncompleter group was missing a Framingham physical activity score.

portions of participants in each intervention who achieved the following levels of weight change over 48 weeks were similar: less than 5% weight loss (LCKD, 36%; O + LFD, 41%), 5% to less than 10% weight loss (LCKD, 19%; O + LFD, 18%), 10% to less than 20% weight loss (LCKD, 31%; O + LFD, 31%), and 20% or greater weight loss (LCKD, 14%; O + LFD, 11%) ( $\chi^2=0.54$ ;  $P=.91$ ). Participants who attended 80% or more of the group counseling sessions lost considerably more weight, regardless of treatment assignment (observed means: LCKD [n=26], -14.9%; O + LFD [n=27], -13.9%).

#### BLOOD PRESSURE AND SERUM LIPID AND LIPOPROTEIN LEVELS

The LCKD participants had greater improvements than O + LFD participants in systolic and diastolic blood pressures (Table 3). For the LCKD participants, change in systolic blood pressure was -5.9 mm Hg (95% CI, -8.8 to -3.1) and diastolic blood pressure was -4.5 mm Hg (95% CI, -6.6 to -2.5), whereas the corresponding

changes for the O + LFD participants were 1.5 mm Hg (95% CI, -0.9 to 3.9) and 0.4 mm Hg (95% CI, -1.3 to 2.2), respectively (Table 3).

The 2 interventions appeared to have differential effects on fasting serum lipid and lipoprotein levels over the first 36 weeks, but these differences converged by 48 weeks (Table 3). The LCKD participants appeared to have greater improvements initially in serum high-density lipoprotein cholesterol and triglyceride levels, whereas the O + LFD participants appeared to have greater improvements initially in serum total and LDL-C levels. However, there were no statistically significant differences between the groups in changes of these measures from baseline to 48 weeks.

#### OTHER METABOLIC EFFECTS

From baseline to 48 weeks, serum urea nitrogen level increased more in the LCKD group than in the O + LFD group (mean difference, 2.0 mg/dL; 95% CI, 0.4 to 3.5) (Table 3). Within the LCKD group, the following para-

**Table 2. Mean (SD) Dietary Energy and Nutrient Intake by Intervention Group and Time Point<sup>a</sup>**

Nutrient	LCKD	O + LFD
Energy, kcal/d		
Baseline	2385 (1050)	2184 (941)
2 wk	1597 (708)	1494 (610)
12 wk	1633 (687)	1577 (749)
24 wk	1723 (697)	1471 (692)
36 wk	1679 (794)	1596 (689)
48 wk	1698 (633)	1566 (777)
Carbohydrates, g/d		
Baseline	262.0 (125.1)	223.0 (112.8)
2 wk	40.1 (47.2)	170.1 (76.4)
12 wk	49.9 (63.3)	188.5 (100.7)
24 wk	54.8 (60.5)	183.4 (95.3)
36 wk	59.0 (55.0)	192.6 (100.9)
48 wk	62.0 (56.3)	186.4 (109.1)
Total fat, g/d		
Baseline	104.9 (60.8)	99.9 (55.3)
2 wk	103.9 (54.0)	54.5 (37.6)
12 wk	103.1 (50.9)	56.5 (40.6)
24 wk	109.2 (49.9)	50.2 (37.1)
36 wk	103.7 (58.3)	57.9 (35.2)
48 wk	106.7 (50.1)	56.9 (40.8)
Saturated fat, g/d		
Baseline	34.2 (21.9)	31.8 (18.8)
2 wk	37.6 (22.3)	16.5 (13.6)
12 wk	36.5 (19.8)	16.4 (11.4)
24 wk	39.2 (22.3)	15.0 (12.7)
36 wk	34.9 (23.2)	17.4 (11.8)
48 wk	37.9 (20.8)	16.6 (12.7)
Monounsaturated fat, g/d		
Baseline	24.5 (19.4)	24.4 (19.3)
2 wk	27.4 (17.8)	13.6 (13.0)
12 wk	25.2 (15.6)	13.9 (14.5)
24 wk	29.6 (16.2)	13.0 (13.2)
36 wk	25.7 (17.8)	13.8 (12.3)
48 wk	27.4 (18.6)	14.7 (16.0)
Polyunsaturated fat, g/d		
Baseline	10.6 (9.8)	10.5 (9.3)
2 wk	8.9 (7.5)	6.3 (6.1)
12 wk	8.8 (7.5)	6.0 (5.7)
24 wk	9.4 (5.9)	6.2 (5.3)
36 wk	8.8 (6.4)	5.6 (4.5)
48 wk	9.2 (6.9)	6.6 (7.1)

(continued)

meters decreased significantly from baseline to week 48: fasting glucose level ( $-9.7 \text{ mg/dL}$ ; 95% CI,  $-16.9$  to  $-2.6$ ), fasting insulin level ( $-7.3 \mu\text{IU/mL}$ ; 95% CI,  $-13.5$  to  $-1.2$  [participants without diabetes only]), and hemoglobin A<sub>1c</sub> ( $-0.3\%$ ; 95% CI,  $-0.5$  to  $-0.1$ ).

## MEDICATION CHANGES

We examined medication changes from baseline to 48 weeks in those individuals who took medication for hypertension or diabetes during the study. For antihypertension medication, 4 of 43 LCKD participants (9%) had an increase (new medication added or dosage of existing medication raised) and 20 (47%) had a decrease (medication discontinued or dosage lowered). In the O + LFD group, 9 of 53 participants (17%) had an increase and 11 (21%) had a decrease in antihypertension medica-

**Table 2. Mean (SD) Dietary Energy and Nutrient Intake by Intervention Group and Time Point<sup>a</sup> (continued)**

Nutrient	LCKD	O + LFD
trans Fat, g/d		
Baseline	2.7 (4.0)	2.2 (3.6)
2 wk	1.1 (1.2)	0.9 (1.8)
12 wk	1.4 (2.5)	1.1 (3.9)
24 wk	1.3 (1.5)	0.6 (1.3)
36 wk	0.9 (1.1)	0.9 (2.6)
48 wk	1.2 (1.4)	0.9 (2.4)
Protein, g/d		
Baseline	95.5 (41.4)	97.1 (45.6)
2 wk	118.2 (54.6)	80.5 (35.3)
12 wk	116.9 (52.2)	78.0 (33.7)
24 wk	119.1 (50.8)	73.8 (35.4)
36 wk	115.3 (56.4)	79.5 (34.6)
48 wk	112.2 (46.8)	78.0 (35.5)
Cholesterol, mg/d		
Baseline	449.8 (315.4)	444.2 (321.4)
2 wk	804.4 (356.6)	288.5 (225.0)
12 wk	740.1 (337.2)	274.7 (208.5)
24 wk	795.8 (385.8)	259.1 (230.3)
36 wk	735.5 (423.9)	251.4 (204.5)
48 wk	721.2 (351.2)	296.2 (284.1)
Fiber, g/d		
Baseline	17.3 (9.5)	15.7 (9.6)
2 wk	5.7 (4.8)	15.6 (10.3)
12 wk	6.2 (5.9)	16.2 (11.0)
24 wk	6.8 (6.1)	16.3 (10.1)
36 wk	7.2 (5.3)	19.0 (11.1)
48 wk	7.6 (5.0)	17.5 (11.6)

Abbreviations: LCKD, low-carbohydrate, ketogenic diet; O + LFD, orlistat plus a low-fat, reduced-calorie diet.

<sup>a</sup>Data presented are unadjusted raw data with no imputations for missing data. Sample sizes for baseline, 2, 12, 24, 36, and 48 weeks are n=71, n=58, n=48, n=48, n=23, and n=31, respectively, for the LCKD and n=73, n=63, n=49, n=50, n=36, and n=34, respectively, for the O + LFD.

tion. For diabetes medication, 1 of 16 LCKD participants (6%) had an increase and 13 (81%) had a decrease, while 1 of 22 O + LFD participants (5%) had an increase and 15 (68%) had a decrease.

## ADVERSE EFFECTS

The following symptomatic adverse effects were reported at least once by more LCKD participants than O + LFD participants: constipation (69% vs 41%;  $P < .001$ ), increased urinary frequency (79% vs 55%;  $P = .003$ ), halitosis (44% vs 19%;  $P = .001$ ), or leg muscle cramps (61% vs 39%;  $P = .01$ ). More O + LFD than LCKD participants reported increased flatus (78% vs 59%;  $P = .01$ ), bowel incontinence (35% vs 17%;  $P = .01$ ), or diarrhea (73% vs 55%;  $P = .02$ ), resulting in discontinuation of orlistat by 1 participant. One participant with diabetes in the LCKD group developed worse proteinuria during the study. Similar proportions from each group reported a hospitalization or emergency department visit for any reason (LCKD, 38%, vs O + LFD, 35%;  $P = .72$ ). There were few serious adverse events that may have been related to the intervention: 1 LCKD participant was hospitalized for syncope attributed to excessive antihypertension medication and 2 O + LFD participants were hospitalized for unstable angina.

**Table 3. Expected Mean Changes in Clinic and Serum Measurements Relative to Baseline for All Participants<sup>a</sup>**

Measurement	LCKD (n=72) <sup>b</sup>	O + LFD (n=74) <sup>b</sup>	LCKD–O + LFD at 48 Weeks	P Value at 48 Weeks
Clinic measures				
Body weight, %				
12 wk	-8.40	-6.80		
24 wk	-10.73	-9.21		
36 wk	-10.06	-9.14		
48 wk	-9.48 (-12.05 to -6.91)	-8.53 (-10.99 to 6.07)	-0.95 (-4.50 to 2.61)	.60
Body weight, kg				
12 wk	-9.68	-7.51		
24 wk	-12.81	-10.42		
36 wk	-12.38	-10.51		
48 wk	-11.37 (-14.84 to -7.89)	-9.62 (-11.94 to -7.29)	-1.75 (-5.90 to 2.40)	.41
Waist circumference, cm				
12 wk	-8.49	-6.36		
24 wk	-11.46	-9.29		
36 wk	-11.47	-9.85		
48 wk	-11.07 (-13.85 to -8.29)	-9.08 (-10.98 to -7.18)	-1.99 (-5.33 to 1.35)	.24
Systolic blood pressure, mm Hg				
12 wk	-1.49	0.37		
24 wk	-2.97	0.75		
36 wk	-4.45	1.12		
48 wk	-5.94 (-8.80 to -3.08)	1.50 (-0.88 to 3.87)	-7.44 (-11.12 to -3.75)	<.001
Diastolic blood pressure, mm Hg				
12 wk	-2.85	-1.70		
24 wk	-4.55	-2.19		
36 wk	-5.11	-1.48		
48 wk	-4.53 (-6.57 to -2.49)	0.43 (-1.34 to 2.21)	-4.97 (-7.64 to -2.29)	<.001
Framingham physical activity index, <sup>16</sup> score				
12 wk	0.6	-0.4		
24 wk	0.1	0.3		
36 wk	-0.4	0.3		
48 wk	-0.2 (-1.4 to 1.0)	0.3 (-0.9 to 1.5)	-0.5 (-2.2 to 1.2)	.58
Blood tests				
Total cholesterol, mg/dL				
12 wk	-4.54	-28.60		
24 wk	2.91	-17.18		
36 wk	-0.21	-19.08		
48 wk	-3.80 (-10.68 to 3.07)	-8.86 (-15.31 to -2.41)	5.05 (-4.37 to 14.48)	.29
Triglycerides, mg/dL <sup>c</sup>				
12 wk	-41.82	-28.82		
24 wk	-42.21	-21.13		
36 wk	-44.95	-27.83		
48 wk	-28.83 (-48.08 to -9.58)	-21.40 (-39.63 to -3.17)	-7.43 (-33.94 to 19.08)	.58
LDL-C, mg/dL				
12 wk	3.12	-20.75		
24 wk	8.09	-13.90		
36 wk	3.19	-15.43		
48 wk	-1.91 (-8.14 to 4.33)	-8.29 (-14.06 to -2.52)	6.39 (-2.11 to 14.88)	.14
HDL-C, mg/dL				
12 wk	1.23	-2.39		
24 wk	4.03	0.29		
36 wk	5.87	1.86		
48 wk	3.77 (1.84 to 5.70)	3.43 (1.61 to 5.25)	0.34 (-2.31 to 3.00)	.80

(continued)

**COMMENT**

In this randomized trial comparing LCKD with O + LFD, we found that the 2 interventions resulted in substantial yet similar weight loss over 48 weeks in an outpatient population. The interventions also had comparable beneficial effects on most measures of cardiovascular disease risk, including waist circumference, fasting serum lipid profiles, and C-reactive protein. The LCKD had a

more favorable effect on blood pressure than the O + LFD in these outpatients, most of whom had hypertension. The improvement in blood pressure in the LCKD group (-5.9/-4.5 mm Hg) was near to that seen in a large cohort of patients who underwent bariatric surgery (approximately -8/-6 mm Hg).<sup>25</sup>

The majority of weight loss for both interventions occurred in the first 12 to 24 weeks with maximum weight loss achieved at 24 to 36 weeks, after which slight weight

**Table 3. Expected Mean Changes in Clinic and Serum Measurements Relative to Baseline for All Participants<sup>a</sup> (continued)**

Measurement	LCKD (n=72) <sup>b</sup>	O + LFD (n=74) <sup>b</sup>	LCKD–O + LFD at 48 Weeks	P Value at 48 Weeks
Blood tests (continued)				
Total cholesterol–HDL-C ratio				
12 wk	-0.27	-0.54		
24 wk	-0.36	-0.49		
36 wk	-0.63	-0.67		
48 wk	-0.44 (-0.68 to -0.20)	-0.51 (-0.73 to -0.28)	0.07 (-0.26 to 0.40)	.68
Triglyceride–HDL-C ratio <sup>c</sup>				
12 wk	-1.30	-0.73		
24 wk	-1.42	-0.67		
36 wk	-1.69	-0.94		
48 wk	-1.00 (-1.65 to -0.35)	-0.77 (-1.38 to -0.15)	-0.23 (-1.12 to 0.66)	.61
C-reactive protein, mg/L				
24 wk	-0.07	-0.05		
48 wk	-0.18 (-0.30 to -0.06)	-0.15 (-0.26 to -0.04)	-0.03 (-0.20 to 0.13)	.69
Hemoglobin A <sub>1c</sub> , %				
24 wk	-0.37	-0.21		
48 wk	-0.30 (-0.52 to -0.09)	-0.06 (-0.26 to 0.14)	-0.24 (-0.54 to 0.05)	.10
Fasting glucose, mg/dL				
12 wk	-8.46	-14.36		
24 wk	-7.88	-6.01		
36 wk	-7.46	-5.33		
48 wk	-9.74 (-16.93 to -2.55)	-3.26 (-10.05 to -3.54)	-6.48 (-16.38 to 3.42)	.20
Fasting insulin, µIU/mL <sup>d</sup>				
12 wk	-8.31	-5.31		
24 wk	-8.54	-6.82		
36 wk	-7.46	-4.01		
48 wk	-7.32 (-13.49 to -1.16)	-2.42 (-8.35 to 3.50)	-4.90 (-13.45 to 3.65)	.26
SUN				
12 wk	2.13	0.72		
24 wk	2.90	-0.52		
36 wk	1.99	0.50		
48 wk	3.19 (2.07 to 4.30)	1.23 (0.17 to 2.29)	1.96 (0.42 to 3.50)	.01
Creatinine				
12 wk	-0.02	0.02		
24 wk	-0.01	-0.01		
36 wk	0.00	-0.01		
48 wk	0.01 (-0.02 to 0.05)	0.00 (-0.03 to 0.04)	0.01 (-0.04 to 0.05)	.72
Urine albumin–creatinine ratio, mg/g of Cr <sup>e</sup>				
24 wk	12.34	-0.31		
48 wk	6.40 (-5.47 to 18.26)	1.18 (-9.86 to 12.22)	5.22 (-10.99 to 21.42)	.52

Abbreviations: Cr, creatinine; HDL-C, high-density lipoprotein cholesterol; LCKD, low-carbohydrate, ketogenic diet; LDL-C, low-density lipoprotein cholesterol; O + LFD, orlistat plus a low-fat, reduced-calorie diet; SUN, serum urea nitrogen.

SI conversion factors: To convert cholesterol and triglycerides to millimoles per liter, multiply by 0.0259 and 0.0113, respectively; C-reactive protein to nanomoles per liter, multiply by 9.524; hemoglobin A<sub>1c</sub> to a proportion of total hemoglobin, multiply by 0.01; glucose to millimoles per liter, multiply by 0.0555; insulin to picomoles per liter, multiply by 6.945; and creatinine to micromoles per liter, multiply by 88.4.

<sup>a</sup>Values are expected means by linear mixed-effects models analysis.

<sup>b</sup>Ninety-five percent confidence intervals are given in parentheses at 48 weeks.

<sup>c</sup>One outlier was removed from the LCKD group where triglyceride level was 687 mg/dL and readings at 3 other time points were below 200 mg/dL.

<sup>d</sup>Fasting serum insulin level is reported for patients who did not have diabetes and were not taking diabetes medication.

<sup>e</sup>One outlier was removed from the LCKD group where urine albumin-creatinine ratio increased from 164 to 1144 mg/g of Cr.

regain occurred. These patterns of weight loss and regain are similar to previous trials that compared the LCKD with an LFD without adjunctive weight loss medication over 1 year.<sup>6,26-28</sup> In the only randomized trial to extend follow-up beyond 1 year, the weight regain in the LCKD arm leveled off early in the second year, and weight loss remained greater than the LFD arm at the end of 2 years.<sup>3</sup>

While the LCKD has lowered blood pressure in other studies, the greater effect compared with the O + LFD was unexpected because the 2 interventions resulted in similar weight loss and because the O + LFD also typically

lowers blood pressure, albeit slightly.<sup>2,29,30</sup> More surprisingly, this effect occurred while antihypertension medication use was decreased more frequently in the LCKD than O + LFD participants. One potential mechanism for blood pressure improvement is that the LCKD may have a diuretic effect. In a previous study, we found that total body water decreased more sharply over the first 2 weeks with the LCKD than the LFD, but the levels remained parallel thereafter.<sup>18</sup> Another mechanism may be related to lower serum insulin levels seen with the LCKD; hyponinsulinemia has been associated with sodium reten-

tion, proliferation of vascular smooth muscle, increased sympathetic nervous system activity, and diminished release of nitric oxide from the endothelium.<sup>31,32</sup>

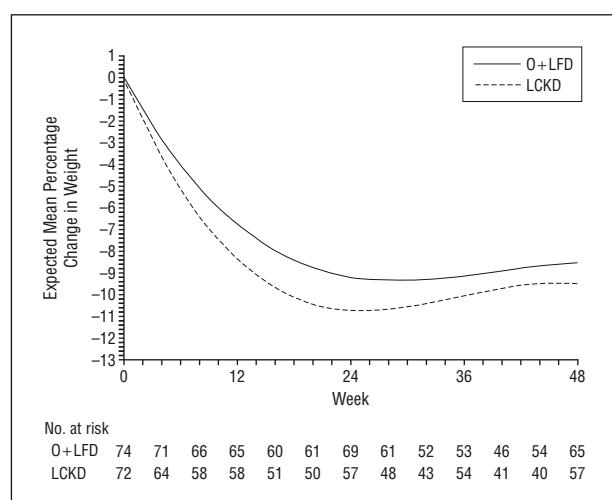
In a meta-analysis of studies comparing the LCKD with an LFD, changes in systolic and diastolic blood pressure favored the LCKD but reached statistical significance for systolic blood pressure only.<sup>2</sup> In the OmniHeart Study, both the high-protein and high-monounsaturated fat diets (the LCKD is high in these macronutrients) lowered systolic and diastolic blood pressures more than the high-carbohydrate, low-fat diet.<sup>33</sup> In view of these data and studies showing that other weight loss medications (eg, sibutramine) typically attenuate the improvement in blood pressure expected from weight loss,<sup>4</sup> the LCKD should be considered in hypertensive patients who desire weight loss.

According to the food records, the 2 interventions resulted in noticeably different macronutrient intakes. Dur-

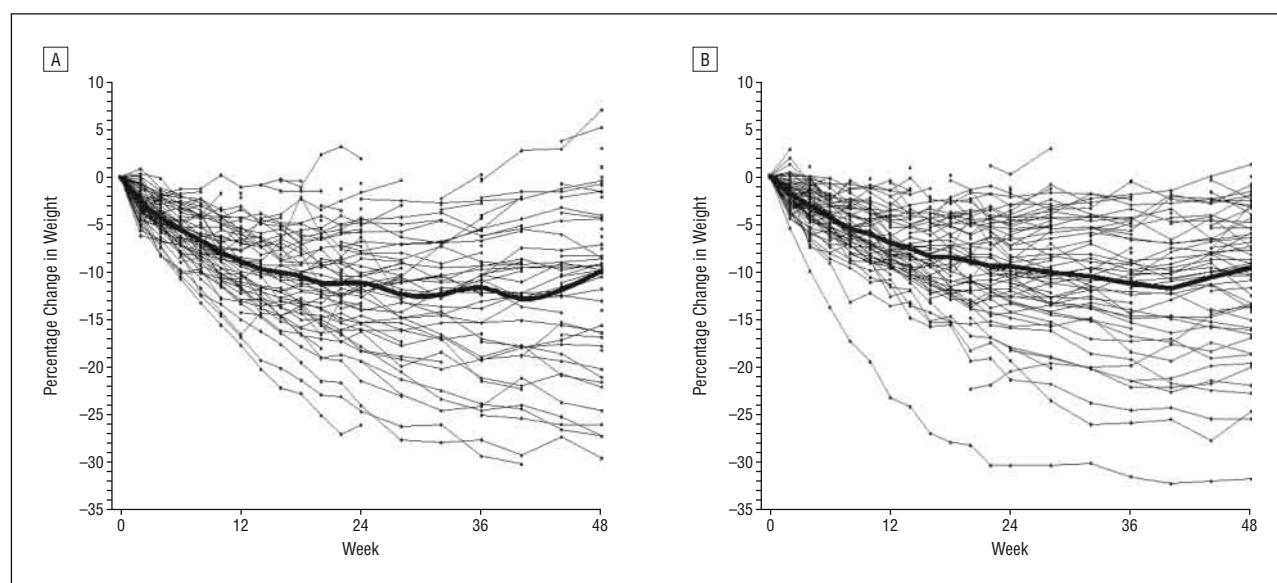
ing the intervention, the LCKD participants obtained more than 55% of their daily calorie intake from fat. Yet, because they also restricted energy intake, the amount of total fat they consumed was actually identical to their baseline diet. However, because the low-fat diet was combined with orlistat, which blocks the absorption of approximately 30% of ingested fat, the O + LFD group decreased their effective fat intake considerably, from approximately 100 g (41% of calories) per day to 35 to 40 g (21%-23% of calories) per day. The study results demonstrate how beneficial health effects can be achieved with either a proportionally very high-fat or very low-fat diet, so long as calorie intake is not high.

Compared with other trials, adherence was high over the 48 weeks. For example, the mean carbohydrate intake was 62 g/d (15% of calorie intake) at week 48 in the LCKD group. In most other trials reporting out to a year, the range was 120 to 190 g/d (33%-45% energy intake).<sup>3,6,26,27,34</sup> Although our data and recent data from Brinkworth et al<sup>35</sup> show that adherence to a low-carbohydrate diet can persist at 1 year, this duration is relatively short compared with the lifetime that many individuals must struggle with weight management. Adherence to either intervention over periods longer than a year has been examined in a few randomized trials, with some recidivism evident.<sup>3,29,30,36,37</sup> To truly have an impact on the obesity problem that our world faces, methods for improving long-term adherence to these and other weight loss strategies must be available.

Although adverse effects occurred with both interventions, participants learned to tolerate or alleviate them in most circumstances. The O + LFD participants reported gastrointestinal adverse effects more frequently than the LCKD participants, but only 1 participant discontinued orlistat treatment due to intolerance. Participants communicated that these adverse effects occurred predominantly after dietary indiscretions. Similarly, the LCKD had its own gastrointestinal adverse effect, constipation. In most cases, constipation resolved by in-



**Figure 2.** Expected mean percentage body weight changes over time by treatment group. Expected mean percentage body weight change estimates determined by linear mixed-effects analysis. LCKD indicates low-carbohydrate, ketogenic diet; O + LFD, orlistat plus a low-fat, reduced-calorie diet.



**Figure 3.** Individual percentage body weight change trajectories by diet group. The bold line represents a smoothed spline of the observed trajectory for the mean percentage body weight change in the low-carbohydrate, ketogenic diet group (A) or the orlistat plus low-fat, reduced-calorie diet group (B).

creasing fluid and dietary fiber intake and/or adding a fiber supplement or stool softener. Our results highlight the importance of combining intensive dietary counseling and medical management with these interventions to maximize weight loss and minimize adverse effects and attrition.

There are limitations to our study. Our goal was to design the interventions so that they closely mimicked a weight loss program that could be instituted in an outpatient clinic. Therefore, we did not provide food, access to exercise facilities, or compensation to participants. We provided orlistat at no cost to participants, and this could have increased dietary adherence, group session attendance, and/or participant retention compared with the LCKD. In addition, providing orlistat at no cost may lead to different results than what might be seen in patients who must pay for orlistat. Because of feasibility issues, we did not blind participants or staff with the resultant potential for bias. The interventions, however, were comparable in all ways possible and measurements were performed as objectively as possible (eg, digital scale with printout, automatic sphygmomanometer). A small number of enrollees discontinued the study before attending their first intervention visit and learning their intervention assignment. By not including them in analyses, our results may slightly overestimate adherence to the interventions. Medication changes could have contributed to some of the observed beneficial effects, but this is unlikely because in order to prevent adverse effects such as dehydration, hypotension, or hypoglycemia, medication use for hypertension and diabetes was more frequently decreased than increased.

In conclusion, the LCKD and the O + LFD were equally effective for weight loss and several cardiovascular disease risk factors, although the low-carbohydrate diet was more effective for lowering blood pressure. Weight loss was substantially greater in participants who attended group sessions regularly, which may indicate the usefulness of these sessions, signify motivated participants, or both. How to identify these select individuals a priori and how to move more individuals into this category is vital to reversing the obesity epidemic. Efforts should be made to incorporate similarly intensive weight loss programs into medical practice.

**Accepted for Publication:** October 2, 2009.

**Correspondence:** William S. Yancy Jr, MD, MHS, Health Services Research and Development Service (Mail Stop 152), Durham VA Medical Center, 508 Fulton St, Durham, NC 27705 (yancy006@mc.duke.edu).

**Author Contributions:** Dr Yancy, together with those responsible for analysis and interpretation of the data, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Yancy, Westman, McDuffie, Grambow, and Oddone. *Acquisition of data:* Yancy, McDuffie, Bolton, and Chalecki. *Analysis and interpretation of data:* Yancy, McDuffie, Grambow, Jeffreys, Bolton, Chalecki, and Oddone. *Drafting of the manuscript:* Yancy, McDuffie, Grambow, and Bolton. *Critical revision of the manuscript for important intellectual content:* Yancy, Westman, McDuffie, Grambow, Jef-

freys, Chalecki, and Oddone. *Statistical analysis:* Grambow and Jeffreys. *Obtained funding:* Yancy and Oddone. *Administrative, technical, and material support:* McDuffie, Bolton, Chalecki, and Oddone. *Study supervision:* Yancy, Westman, Grambow, and Chalecki.

**Financial Disclosure:** Drs Yancy and Westman have received grants from the Robert C. Atkins Foundation to perform clinical research.

**Funding/Support:** Funding for this study was provided by the Department of Veterans Affairs (CLIN-5-03F). Dr Yancy is supported by a VA Health Services Research Career Development Award (RCD 02-183-1).

**Role of the Sponsor:** The sponsor had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

**Additional Contributions:** Marjorie Foy, MA, Dawn Penn, PhD, Shoshana Ungerleider, Beatrice Hong, MD, and Alex Cho, MD, MBA, assisted with the interventions and data collection; Maren Olsen provided statistical expertise during study design and data analysis; and a data and safety monitoring board (David Edelman, MD, Morris Weinberger, PhD, and Kevin Anstrom, PhD) reviewed the study protocol.

## REFERENCES

1. Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med.* 2006;166(3):285-293.
2. Hession M, Rolland C, Kulkarni U, Wise A, Broom J. Systematic review of randomized controlled trials of low-carbohydrate vs low-fat/low-calorie diets in the management of obesity and its comorbidities. *Obes Rev.* 2009;10(1):36-50.
3. Shi I, Schwarzfuchs D, Henkin Y, et al; Dietary Intervention Randomized Controlled Trial (DIRECT) Group. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med.* 2008;359(3):229-241.
4. Yanovski SZ, Yanovski JA. Obesity. *N Engl J Med.* 2002;346(8):591-602.
5. Boden G, Sargrad K, Homko C, Mozzoli M, Stein TP. Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. *Ann Intern Med.* 2005;142(6):403-411.
6. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA.* 2005;293(1):43-53.
7. Nielsen JV, Jonsson E, Nilsson AK. Lasting improvement of hyperglycaemia and bodyweight: low-carbohydrate diet in type 2 diabetes: a brief report. *Ups J Med Sci.* 2005;110(2):179-183.
8. Yancy WS Jr, Foy M, Chalecki AM, Vernon MC, Westman EC. A low-carbohydrate, ketogenic diet to treat type 2 diabetes. *Nutr Metab (Lond).* December 1 2005; 2:34.
9. Samaha FF, Iqbal N, Seshadri P, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med.* 2003;348(21):2074-2081.
10. Bantle JP, Wylie-Rosett J, Albright AL, et al; American Diabetes Association. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care.* 2008;31(suppl 1):S61-S78.
11. National Institutes of Health, National Heart Lung and Blood Institute, North American Association for the Study of Obesity. *The Practical Guide: Identification, Evaluation and Treatment of Overweight and Obesity in Adults.* Washington, DC: US Dept of Health and Human Services, Public Health Service; 2000. NIH publication 00-4084.
12. *The Atkins Trial Kit Handbook: A Simple Guide to Doing Atkins.* Ronkonkoma, NY: Atkins Nutritionals Inc; 2001.
13. Borushek A. *The Doctor's Pocket Calorie, Fat & Carbohydrate Counter.* Costa Mesa, CA: Family Health Publications; 2004.
14. American Dietetic Association. *Low-Fat Living.* Chicago, IL: American Dietetic Association; 2004.
15. Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids.* Washington, DC: National Academies Press; 2002.

16. Kannel WB, Sorlie P. Some health benefits of physical activity: the Framingham Study. *Arch Intern Med.* 1979;139(8):857-861.
17. Friedewald WT, Levy RI, Fredericson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without the use of the preparative ultracentrifuge. *Clin Chem.* June 1972;18(6):499-502.
18. Yancy WS Jr, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Ann Intern Med.* 2004;140(10):769-777.
19. Donner A, Klar N. *Design and Analysis of Cluster Randomized Trials in Health Research.* New York, NY: Oxford University Press; 2000.
20. International Conference on Harmonisation E9 Expert Working Group. ICH Harmonised Tripartite Guideline: statistical principles for clinical trials. *Stat Med.* 1999; 18(15):1905-1942.
21. Verbeke G, Molenberghs G. *Linear Mixed Models for Longitudinal Data.* New York, NY: Springer-Verlag; 2000.
22. Burnham KP, Anderson DR. *Model Selection and Multi-Model Inference: A Practical Information Theoretic Approach.* 2nd ed. New York, NY: Springer; 2002.
23. Little R, Milliken G, Stroup W, Wolfinger R, Schabenberger O. *SAS for Mixed Models.* 2nd ed. Cary, NC: SAS Institute Inc; 2006.
24. Little RJA, Rubin DB. *Statistical Analysis With Missing Data.* 2nd ed. New York, NY: Wiley; 2002.
25. Sjöström CD, Pelttonen M, Sjöström L. Blood pressure and pulse pressure during long-term weight loss in the obese: the Swedish Obese Subjects (SOS) Intervention Study. *Obes Res.* 2001;9(3):188-195.
26. Gardner CD, Kiazyk A, Alhassan S, et al. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. *JAMA.* 2007;297(9):969-977.
27. Stern L, Iqbal N, Seshadri P, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med.* 2004;140(10):778-785.
28. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med.* 2003;348(21):2082-2090.
29. Davidson MH, Hauptman J, DiGirolamo M, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA.* 1999;281(3):235-242.
30. Sjöström L, Rissanen A, Andersen T, et al; European Multicentre Orlistat Study Group. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *Lancet.* 1998;352(9123): 167-172.
31. Passa P. Hyperinsulinemia, insulin resistance and essential hypertension. *Horm Res.* 1992;38(1-2):33-38.
32. Singer GM, Setaro JF. Secondary hypertension: obesity and the metabolic syndrome. *J Clin Hypertens (Greenwich).* 2008;10(7):567-574.
33. Appel LJ, Sacks FM, Carey VJ, et al; OmniHeart Collaborative Research Group. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. *JAMA.* 2005; 294(19):2455-2464.
34. McAuley KA, Smith KJ, Taylor RW, McLay RT, Williams SM, Mann JI. Long-term effects of popular dietary approaches on weight loss and features of insulin resistance. *Int J Obes (Lond).* 2006;30(2):342-349.
35. Brinkworth GD, Noakes M, Buckley JD, Keogh JB, Clifton PM. Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. *Am J Clin Nutr.* 2009;90(1):23-32.
36. Richelsen B, Tonstad S, Rossner S, et al. Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients: a 3-year randomized, placebo-controlled study. *Diabetes Care.* 2007; 30(1):27-32.
37. Hauptman J, Lucas C, Boldrin MN, Collins H, Segal KR. Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med.* 2000;9(2):160-167.

### Correction

**Omission of Affiliation Information.** In the Editorial titled “Can the Food and Drug Administration Ensure That Our Pharmaceuticals Are Safely Manufactured?” by Hubbard, published in the October 12 issue of the Archives (2009;169[18]:1655-1656), it should have been noted that Mr Hubbard is a former FDA Associate Commissioner and a former member of the group Alliance for a Stronger FDA. This omission was due to editorial oversight, and the journal apologizes for the error.



Article

# Greater Loss of Central Adiposity from Low-Carbohydrate versus Low-Fat Diet in Middle-Aged Adults with Overweight and Obesity

Valene Garr Barry <sup>1,\*</sup>, Mariah Stewart <sup>1</sup>, Taraneh Soleymani <sup>1</sup>, Renee A. Desmond <sup>2</sup>, Amy M. Goss <sup>1</sup> and Barbara A. Gower <sup>1</sup>

<sup>1</sup> Department of Nutrition Sciences, School of Health Professions, The University of Alabama at Birmingham, 1720 University Blvd, Birmingham, AL 35294, USA; amc3321@uabmc.edu (M.S.); soltar@uab.edu (T.S.); amymiski@uab.edu (A.M.G.); bgower@uab.edu (B.A.G.)

<sup>2</sup> Division of Preventive Medicine, The University of Alabama at Birmingham, Medical Towers 621, 1717 11th Avenue South, Birmingham, AL 35205, USA; rdesmond@uabmc.edu

\* Correspondence: vgarr@uab.edu

**Abstract:** The objective of this study is to determine whether middle-aged adults prescribed a low carbohydrate-high fat (LCHF) or low fat (LF) diet would have greater loss of central fat and to determine whether the insulin resistance (IR) affects intervention response. A total of 50 participants ( $52.3 \pm 10.7$  years old;  $36.6 \pm 7.4 \text{ kg/m}^2$  BMI; 82% female) were prescribed either a LCHF diet ( $n = 32$ , carbohydrate: protein: fat of 5%:30%:65% without calorie restriction), or LF diet ( $n = 18$ , 63%:13–23%: 10–25% with calorie restriction of total energy expenditure—500 kcal) for 15 weeks. Central and regional body composition changes from dual-x-ray absorptiometry and serum measures were compared using paired *t*-tests and ANCOVA with paired contrasts. IR was defined as homeostatic model assessment (HOMA-IR)  $> 2.6$ . Compared to the LF group, the LCHF group lost more android ( $15.6 \pm 11.2\%$  vs.  $8.3 \pm 8.1\%$ ,  $p < 0.01$ ) and visceral fat ( $18.5 \pm 22.2\%$  vs.  $5.1 \pm 15.8\%$ ,  $p < 0.05$ ). Those with IR lost more android and visceral fat on the LCHF versus LF group ( $p < 0.05$ ). Therefore, the clinical prescription to a LCHF diet may be an optimal strategy to reduce disease risk in middle-aged adults, particularly those with IR.

**Keywords:** weight loss; low-carbohydrate diet; insulin resistance; visceral fat; DXA



**Citation:** Garr Barry, V.; Stewart, M.; Soleymani, T.; Desmond, R.A.; Goss, A.M.; Gower, B.A. Greater Loss of Central Adiposity from Low-Carbohydrate versus Low-Fat Diet in Middle-Aged Adults with Overweight and Obesity. *Nutrients* **2021**, *13*, 475. <https://doi.org/10.3390/nu13020475>

Academic Editor: Katerina Vafeiadou  
Received: 23 November 2020

Accepted: 25 January 2021  
Published: 31 January 2021

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2021 by the authors. Licensee MDPI, Basel, Switzerland.  
This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Overweight and obesity substantially increase the risk of adverse health events for middle-aged and older adults, such as heart attacks, strokes, and diabetes [1]. The growing obesity epidemic has increasingly led healthcare providers to prescribe dietary interventions to mitigate such poor outcomes. However, choosing the best dietary intervention for those with advanced age remains controversial [2]. An optimal weight loss intervention to reduce disease risk in these populations should target central fat depots, which are pathogenic and grow at a higher rate relative to total body fat in people with advanced age [3]. Additionally, interventions should consider age-specific health concerns, such as the preservation of lean mass and improvement of dyslipidemia and dysglycemia to prevent sarcopenia and reduce disease risk, respectively [2,4]. Yet, there is limited evidence that indicates how particular diet interventions affect these age-specific targets among middle-aged to older adults [2,5].

A low carbohydrate-high fat (LCHF) diet may be ideal for weight loss in an older population. LCHF diets restrict carbohydrate consumption to < 45% of energy intake and emphasize limits on starch and sugar, while encouraging the consumption of healthy (mono- and polyunsaturated) fats and the maintenance of moderate protein intake [6,7]. LCHF diets are known for rapid weight loss with a greater reduction in body fat and

preservation of lean mass, compared to diets that are lower in fat [7–9]. Further, LCHF diets have been associated with a preferential loss of visceral and ectopic fat among younger adults and limited evidence supports similar benefits in older adults [10]. Such results would be ideal for older adults and would mitigate concerns about sarcopenia while targeting the most metabolically harmful fat depots. However, the existing evidence is insufficient to determine whether this diet response is consistent across age groups [2,10].

LCHF diets may also be ideal for individuals with insulin resistance, a condition that is common among older adults and is associated with higher cardiometabolic disease risk [11,12]. Insulin resistance occurs in concert with compensatory hyperinsulinemia, which may prevent mobilization of fatty acids when weight loss is attempted. The lower carbohydrate content of the LCHF diet is believed to reduce insulin secretion, which may permit greater lipolysis and fat oxidation during negative energy balance [7]. In support of this hypothesis, studies that have stratified participants by either insulin resistance or fasting insulin have showed that diet intervention outcomes differ according to phenotype, and that those with insulin resistance responded better to low-carbohydrate diets [13–15]. However, similar studies have not been conducted in middle-aged to older adults [2,16].

The primary objective of this study was to examine whether changes in regional fat and lean mass (kg) differed between middle-aged and older adults with overweight and obesity that were prescribed either a LCHF or LF diet for 15 weeks. Our second objective was to determine whether insulin resistance status affected changes in body composition following the intervention period. We hypothesized that a LCHF diet would result in greater loss of total and central fat mass with lower loss of lean mass, compared to LF, and that this response would be particularly pronounced in individuals with insulin resistance.

## 2. Materials and Methods

### 2.1. Participants and Recruitment

Between May 2014 and January 2017, participants were recruited from a medically supervised weight loss clinic at The University of Alabama at Birmingham (UAB). Additionally, participants were recruited by flyer, newspaper, web-based advertisement, and word of mouth. Eligible participants had a body mass index (BMI)  $\geq 25 \text{ kg/m}^2$ , had been weight stable ( $<10$  pounds gained or lost) in the prior 12 months, and were not actively engaged in an exercise program. Participants with type 2 diabetes were eligible if they were not insulin dependent. Exclusion criteria included age  $> 75$  years, BMI  $> 50 \text{ kg/m}^2$ , current smoking, pregnancy, or breastfeeding. Eligibility was determined during a telephone screening session and confirmed during an in-person screening visit, where participants were also informed of the study procedures and provided both verbal and written consent. The UAB Institutional Review Board (IRB) approved this study.

The goal of these analyses was to examine the effects of diet prescriptions on middle-aged to older (45–75 years) adults. To detect a visceral fat loss of  $11.1 \pm 8.8\%$  with a two-sided 5% significance level and a power of 80%, a sample of 24 participants per group were necessary. We anticipated a dropout rate of 25%.

Some participants younger than 45 were recruited. Given the target age range, we conducted analyses both with and without participants younger than 45 ( $n = 7$ ; 5 LCHF, 2 LF). We observed no differences in study outcomes when younger participants were omitted. Thus, all participants who completed baseline and follow-up assessments were included in the analysis. Participants with missing outcome data were omitted [17].

### 2.2. Diet Prescriptions

#### 2.2.1. Low-Carbohydrate High-Fat Diet (LCHF)

The LCHF prescription had a target macronutrient ratio (carbohydrate: protein: fat) of 5%:30%:65% of total energy, and encouraged increased monounsaturated and polyunsaturated fat intake. At initiation, participants were instructed to consume three meals per day with up to two snacks per day. Daily carbohydrate was limited to no more than 20 total grams per day with 12–15 g from vegetables. The LCHF guidelines and corresponding

meal plans recommended four ounces of protein with each meal, four ounces of dairy per day, one cup cooked non-starchy vegetables daily, two cups leafy vegetables daily, and additional energy needs should come from healthy fats such as  $\frac{1}{2}$  an avocado, olives, and olive oil. After eight weeks with the LCHF prescription, participants were allowed to increase carbohydrate intake to 30 g per day and were allowed to add nuts, nut butters, and berries into their diets.

### 2.2.2. Low-Calorie Low-Fat Diet (LF)

The LF diet prescription had a target a macronutrient ratio (carbohydrate: protein: fat) of 63%:13–23%:10–25% of total energy and restricted calories to 1200–1600 kcal per day based on a 500 kcal reduction from baseline resting energy expenditure (REE) \*1.3 [18]. The LF diet emphasized the consumption of low energy density foods, appropriate portion control, and specified low fat food options to meet energy needs. The LF guidelines and corresponding meal plans recommend that where possible, participants chose vegetables over fruit, and fruit over starches. Likewise, guides recommend that participants consume dairy more often than meat or protein sources, and meat or protein more often than fat.

### 2.2.3. Diet Selection and Adherence

After reviewing guidelines for both diets with a registered dietitian (RD), participants consulted with a weight loss medicine physician to choose their diet prescription. Then an RD provided diet instructions, sample meal plans, and recipes to aid participants with adhering to their respective diet. In addition, participants were offered weekly group lifestyle management classes that provided accountability and discussed topics such as Quick Cooking and Meal Assembly, Mindful Eating, and Healthy Substitutions on LCHF or LF. Diet adherence was monitored via 3-day food records and body weight by the study physician and RD at dedicated follow-up sessions that occurred at +2 weeks, +4 weeks, +8 weeks, +12 weeks, and +15 weeks.

## 2.3. Study Outcomes and Tests

Study outcomes were assessed before (within one week) diet initiation and after 15 weeks of the intervention, which included standard anthropometrics, fasting serum measures, REE, and body composition. All measurements and tests were completed in the Core facilities of the Center for Clinical and Translational Science (CCTS), Nutrition Obesity Research Center (NORC), and Diabetes Research Center (DRC) at UAB. Participants were instructed to fast for at least 10 h (overnight) before each study visit, maintain their usual activity level, to avoid strenuous exercise the day before testing, and avoid exercise on the morning of testing.

### 2.3.1. Body Composition

Total and regional fat and lean mass were assessed using dual X-ray absorptiometry (DXA) (Lunar iDXA, enCORE version 13.6, GE Medical Systems, Madison, WI, USA) [19–21] using manufacturer defined regions of interest (ROI), which are described in detail elsewhere [21,22]. Fat and lean mass were analyzed for each of the following regions: (1) total body, which includes all regions in the scan; (2) trunk, which includes neck, chest, abdominal, and pelvic areas; (3) android, which includes the area between ribs and pelvis (totally enclosed inside the trunk); (4) gynoid, which includes hips and upper thighs, and overlaps with both legs and trunk; and (5) appendicular, which includes arms (and shoulder) and leg regions [19,21]. Visceral fat was estimated using the CoreScan algorithm (GE Medical Systems, Madison, WI, USA), which subtracts subcutaneous fat from total android fat to yield an estimate of visceral fat [23].

### 2.3.2. Resting Energy Expenditure

REE and respiratory quotient (RQ) were measured using a VMAX ENCORE 29N indirect calorimeter [VIASYS Respiratory Care, Inc. (formerly Sensormedics), Palm Springs, CA] following an overnight fast and a 15-min supine rest.

### 2.3.3. Glucose, Insulin and Lipids

Fasting blood draws were performed at each study visit to measure glucose, insulin, and lipids. Glucose and lipids were analyzed using the SIRRUS analyzer (Stanbio Laboratory, Boerne, TX, USA). Glucose was measured in 3  $\mu$ L sera using the glucose oxidase method. This analysis had an intra-assay coefficient of variation (CV) of 1.2% and inter-assay CV of 3.1%. Insulin was assayed in 50  $\mu$ L aliquots using immunofluorescence technology on a TOSOH Automated Immunoassay Analyzer II (AIA-II) analyzer (TOSOH Corp., South San Francisco, CA, USA). This analysis had an intra-assay CV of 1.5% and inter-assay CV of 4.4%. Insulin and glucose were used to quantify insulin resistance according to the homeostatic model assessment of insulin resistance (HOMA-IR) [24]. Insulin resistance was defined as HOMA-IR > 2.6 [25]. Baseline glycated hemoglobin (HbA1C) > 6.5% was used to denote diabetes [26].

## 2.4. Statistical Analysis

Baseline descriptive statistics (means  $\pm$  SD) were compared between groups using the Student's *t*-tests for continuous variables and the Fisher's exact test for categorical variables. Serum measures that were not normally distributed were log-transformed for analyses. Change values (follow-up–baseline) for regional fat mass, lean mass, and serum measures were evaluated for by paired *t*-tests and compared between-groups using analysis of covariance (ANCOVA) controlling for the respective baseline measure, age (years), sex, and race and ethnicity. Due to our small sample size, this study was not powered to test for interactions of insulin resistance status with every outcome. Therefore, the effects of insulin resistance phenotype on the response to the intervention were explored with subgroup analysis via pairwise contrasts. Statistical significance was specified as  $p \leq 0.05$ .

## 3. Results

### 3.1. Baseline Characteristics

In total, 80 participants enrolled in the study and chose either the LCHF ( $n = 48$ ) or LF ( $n = 32$ ) diet. The overall study completion rate was 63% ( $n = 50$ ) and was not statistically different between groups; 67% ( $n = 32$ ) for the LCHF and 56% ( $n = 18$ ) for the LF group. The baseline characteristics were not significantly different between completers and non-completers.

The participants (henceforth, meaning those who completed the study) were 82% ( $n = 41$ ) women and 74% ( $n = 37$ ) European Americans with a mean age of  $52 \pm 10$  years. At baseline, 52% ( $n = 26$ ) of participants were insulin-resistant (HOMA-IR > 2.6) and 14% ( $n = 7$ ) had diabetes (HbA1c > 6.5). The participants' baseline characteristics were not significantly different between the LCHF and LF groups (Table 1). Self-reported medication use and medical history are shown in the supplementary materials (Tables S1 and S2).

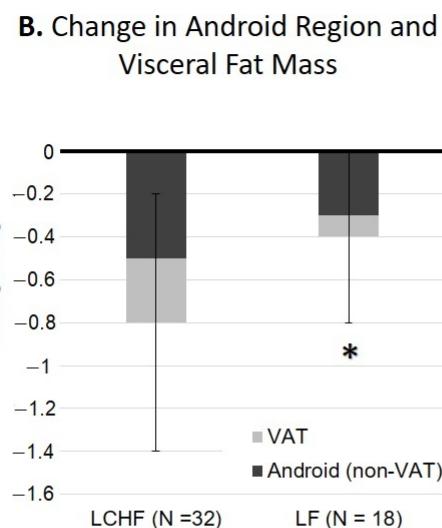
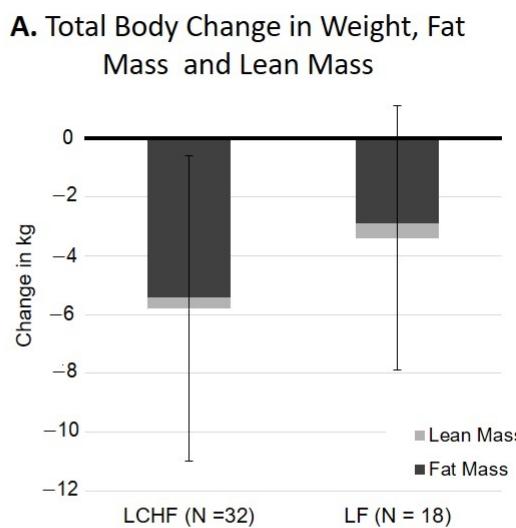
**Table 1.** Baseline Characteristics of Participants by Intervention ( $n = 50$ ).

	LCHF Diet (n = 32)	LF Diet (n = 18)	p-Value
Age, years	52.8 (2.1)	48.4 (10.3)	0.69
BMI, kg/m <sup>2</sup>	36.3 (7.6)	37.4 (6.9)	0.61
REE, kcal/day	1562.6 (275.8)	1613.7 (339.6)	0.33
Gender, %			
Female	81.3	83.3	
Male	18.8	16.7	0.85
Race, %			
European American	81.3	61.1	
African American	18.8	38.9	0.12
Insulin Resistance, %			
HOMA-IR < 2.6 (IS)	70.8	57.7	
HOMA-IR ≥ 2.6 (IR)	29.1	42.3	0.39
Diabetes, %			
HbA1C > 6.5	87.5	83.33	
HbA1C ≤ 6.5	12.5	16.37	0.69
Regular Exercise, %			
Yes	42.9	31.3	
No	57.1	68.8	0.53
Dropouts, %	31.9	43.8	0.28

Data given as mean (SD) or percentage; IS—Insulin-sensitive; IR—Insulin-resistant.

### 3.2. Total Fat and Lean Mass Loss

At follow-up, participants in both groups had a significant decrease in total body weight and total body fat mass, but maintained total body lean mass (Table 2). The LCHF group lost  $6.1 \pm 5.2$  kg ( $5.4 \pm 3.6$  kg fat), and the LF group lost  $3.1 \pm 4.5$  kg ( $3.0 \pm 3.2$  kg fat). There were no significant differences in weight, total fat, or total lean mass changes between diet groups (Figure 1A).



**Figure 1.** Age, sex, and race, adjusted comparison of change in body composition by diet group. (A) Change in weight (total bar), fat mass (dark-filled segment) and lean mass (light-filled segment). (B). Change in android region fat mass (total bar), non-visceral android fat (dark-filled segment) and visceral fat (VAT) mass (light-filled segment). Compared to the Low-carbohydrate high fat (LCHF) group, the low-fat (LF) had lower changes in android regions and visceral fat. \* ( $p < 0.05$ ).

**Table 2.** Comparison of Baseline and Follow-Up (15 week) Measures by Paired *t*-test Within Each Diet Group and ANCOVA Between Diet Groups.

	LCHF Diet (n = 32)		LF Diet (n = 18)		p-Value
	Baseline	Follow-Up	Baseline	Follow-Up	
<b>Demographics</b>					
Weight, kg	100.1 (24.7)	94.0 (24.1) ***	105.3 (18.9)	102.1 (19.4) **	0.1615
BMI, kg/m <sup>2</sup>	36.1 (7.7)	33.9 (7.4) ***	37.4 (6.9)	36.3 (7.1) **	0.1713
Fat, %	45.3 (7.4)	42.6 (7.7) ***	45.8 (5.2)	44.3 (5.3) ***	0.0864
REE, kcal/day	1562.6 (275.8)	1531 (285.7)	1613.7 (339.6)	1556.3 (304.9)	0.1199
<b>Region Fat Mass—DXA</b>					
Total Fat, kg	46.1 (15.8)	40.7(15.0) ***	48.7 (13.2)	45.8 (12.9) **	0.055
Appendicular Fat, kg	20.3 (8.7)	23.6 (6.4) ***	21.7 (6.8)	20.6 (7.1) **	0.193
Trunk Fat, kg	25.3 (9.1)	21.9 (8.1) ***	26.0(7.7)	24.2 (7.2) **	<b>0.049</b>
Android Fat, kg	4.6 (1.8)	3.9 (1.6) ***	4.7 (1.4)	4.3 (1.4) ***	<b>0.027</b>
Gynoid Fat, kg	7.8 (3.0)	6.8 (2.9) ***	7.9 (2.7)	7.4 (2.5) **	0.068
Visceral Fat, kg	1.6 (1.3)	1.4 (1.0) ***	1.8 (0.9)	1.6 (0.9)	<b>0.019</b>
<b>Region Lean Mass—DXA</b>					
Total lean, kg	50.6 (11.4)	50.1 (1.2)	52.7 (7.2)	52.4 (7.7)	0.997
Trunk lean, kg	23.7 (5.5)	23.3 (5.7) *	24.0 (3.1)	23.8 (3.3)	0.804
Android lean, kg	3.8 (1.0)	3.7 (1.0) **	3.8 (0.6)	3.8 (0.6)	0.542
Gynoid lean, kg	8.1 (1.9)	7.8 (1.9) **	8.1 (1.1)	8.1(1.2)	0.250
Appendicular lean, kg	23.7 (5.8)	23.6 (6.4)	25.3 (4.3)	25.3 (4.5)	0.996
<b>Serum Analytes</b>					
Glucose, mg/dL	109.4 (39.6)	103.4 (12.6)	107.7 (33.5)	116.7 (59.4)	0.2529
Insulin, $\mu$ U/mL	14.0 (9.1)	12.3(8.2)	18.0 (11.1)	21.5 (18.2)	0.1230
HOMA-IR	4.0 (3.4)	3.2 (2.4) ***	5.4 (5.7)	6.3 (5.9) *	0.0627
Triglycerides, mg/dL	121.0 (69.1)	96.0 (61.1) *	134.9 (75.3)	132.3 (83.7)	0.0875
HDL, mg/dL	66.1 (16.6)	65.3 (16.2)	58.1(16.2)	58.5 (12.5)	0.9360
LDL, mg/dL	113.0 (26.6)	113.5 (30.5)	101.3 (36.3)	104.4 (30.1)	0.3278
Total cholesterol, mg/dL	203.3 (31.1)	198.0 (35.8)	186.4 (35.8)	184.3 (30.8)	0.6262

Data given as mean (SD); DXA—Dual X-ray-Absorptiometry; \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$  for paired-t test comparing baseline and follow-up.  $p$  value for ANCOVA comparison of change variable between LCHF and LF groups, controlling for age, sex, race, and baseline measures. Bold  $p$ -values indicate significant.

### 3.3. Regional Fat and Lean Mass Loss

Both groups had a significant decrease in trunk, android, and gynoid fat mass (Table 2). The LCHF group had a significant decrease in visceral fat ( $p < 0.001$ ). The LF group did not have any significant change in visceral fat ( $p = 0.40$ ). Compared to the LF group, the LCHF group had significantly greater loss of visceral fat ( $18.5 \pm 22.2\%$  vs.  $5.1 \pm 15.8\%$ ,  $p < 0.05$ ) and total android region fat ( $15.6 \pm 11.2\%$  vs.  $8.3 \pm 8.1\%$ ,  $p < 0.01$ ) (Figure 1B). However, there were no significant differences in loss of gynoid or appendicular fat mass between the groups. With respect to lean mass, the LCHF group lost lean mass in the trunk ( $p < 0.05$ ), android ( $p < 0.01$ ), and gynoid ( $p < 0.01$ ) regions, but maintained total body and appendicular lean mass. In contrast, the LF group did lose a significant amount of lean mass in any region (Table 2).

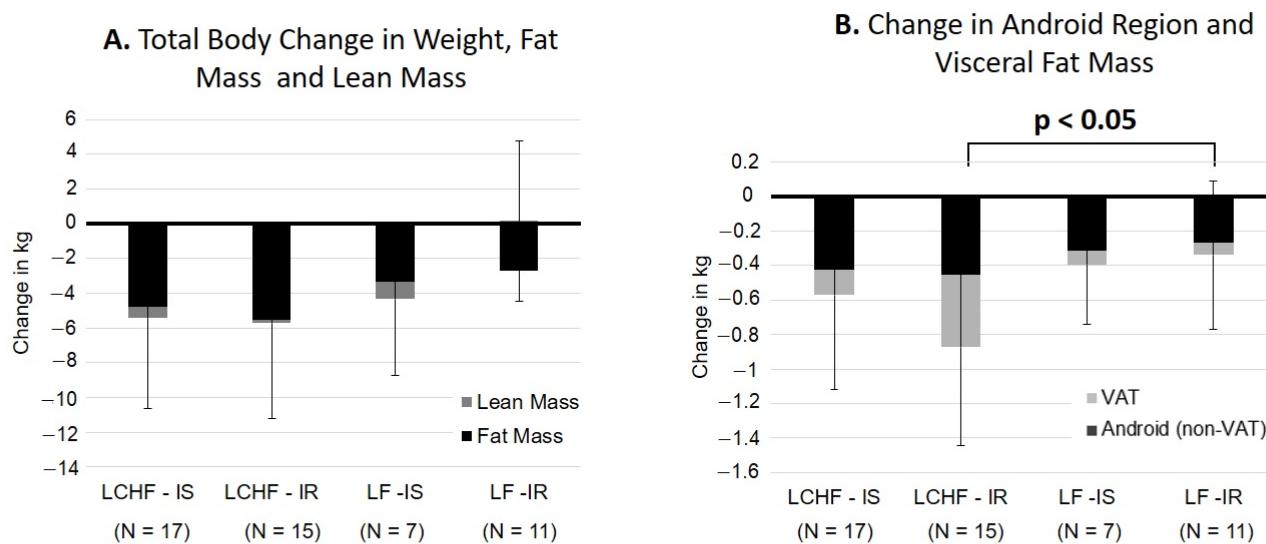
### 3.4. Serum Measures

In the LCHF group, HOMA-IR significantly decreased ( $p < 0.001$ ). Conversely, in the LF group, HOMA-IR significantly increased ( $p < 0.05$ ) (Table 2). Although potentially clinically relevant, the difference between groups for the change of HOMA-IR (LCHF:  $-0.8$  HOMA units vs. LF + 0.9 HOMA units) did not quite reach statistical significance ( $p = 0.06$ ).

All other serum measures were similar to their baseline values in both groups and were not significantly different between groups (Table 2).

### 3.5. Subgroup Analysis by Insulin Resistance Status

Between-group contrasts showed that insulin-resistant participants in the LCHF group lost significantly more android and visceral fat than insulin-resistant participants in the LF group ( $p < 0.05$ ) (Figure 2B). Although not significant, insulin-resistant participants in the LF group gained visceral fat. Insulin-resistant individuals in the LCHF diet had a greater decrease in fasting insulin and HOMA-IR, compared to the LF group ( $p < 0.05$ ). Conversely, there were no differences for changes in central fat mass, lean mass, or serum measures between insulin-sensitive participants that were prescribed to different diets (Table 3). Table 3 provides change values for each phenotype-diet group and  $p$ -values for each comparison.



**Figure 2.** Age, sex, and race, adjusted comparison of change in body composition by diet group and insulin resistance phenotype. (A) Change in weight (total bar), fat mass (dark-filled segment), and lean mass (light-filled segment). (B) Change in android region fat mass (total bar), non-visceral android fat (dark filled segment) and visceral fat mass (light-filled segment). Changes in android regions and visceral fat were lower among insulin-resistant participants in the LF group versus the LCHF group ( $p < 0.05$ ).

**Table 3.** Comparison of change between baseline and follow up by insulin sensitivity and diet group with pairwise contrast within and between diet group.

	LCHF Diet (n = 32)		LF Diet (n = 18)		Within Diet Contrasts		Between Diet Contrasts	
	Insulin Resistant (n = 17)	Insulin Sensitive (n = 15)	Insulin Resistant (n = 11)	Insulin Sensitive (n = 7)	IR vs. IS	IR vs IS	LCHF vs. LF	LCHF vs. LF
<b>Demographics</b>								
Weight, kg	-6.3 (5.3)	-6.0 (5.2)	-2.5 (4.6)	-4.2 (4.4)	0.7730	0.4432	0.0761	0.3207
BMI, kg/m <sup>2</sup>	-2.2 (1.9)	-2.2 (2.0)	-0.9 (1.8)	-1.4 (1.4)	0.7479	0.5400	0.0896	0.2694
Fat, %	-2.7 (3.0)	-2.8 (2.7)	-1.4 (1.1)	-1.6 (1.9)	0.9672	0.8715	0.1682	0.2785
REE, kcal/day	-46.2 (223.4)	3.9 (134.3)	-92.4 (14.6)	-38.2 (140)	0.7855	0.5209	0.2949	0.6271

**Table 3.** Cont.

LCHF Diet (n = 32)		LF Diet (n = 18)		Within Diet Contrasts		Between Diet Contrasts	
Insulin Resistant (n = 17)	Insulin Sensitive (n = 15)	Insulin Resistant (n = 11)	Insulin Sensitive (n = 7)	LCHF Diet	LF Diet	IR	IS
<b>Serum Analytes</b>							
Glucose, mg/dL	−17.3 (45.3)	3.9 (7.6)	13.6 (39.5)	1.6 (12.3)	0.1702	0.3926	0.1093
Insulin, µU/mL	−6.4 (8.8)	2.5 (7.5)	2.5 (19.9)	5 (10.9)	0.1016	0.7273	0.0827
HOMA–IR	−2.4 (3.8)	0.7 (1.9)	0.8 (6.1)	1.2 (2.5)	0.8911	0.8608	0.0267 *
Triglycerides, mg/dL	−42.6 (79.2)	−9.6 (27.9)	−5.6 (64.9)	2.1 (21.8)	0.2057	0.8310	0.0614
HDL, mg/dL	−2.4 (8.6)	0.6 (10.2)	3.6 (8.1)	−4.7 (9.4)	0.0448 *	0.5996	0.3598
LDL, mg/dL	1.5 (35.4)	−0.4 (22.2)	−0.3 (10.5)	−3.4 (26.0)	0.5551	0.7674	0.9664
Total cholesterol, mg/dL	−9.5 (34.5)	−1.7 (25.9)	−1.5 (15.3)	−7.7 (21.8)	0.1132	0.5854	0.3945
<b>Region Fat Mass—DXA</b>							
Total Fat, kg	−6.0 (3.4)	−4.8 (3.8)	−2.7 (3.1)	−3.4 (3.5)	0.7579	0.6532	0.1341
Appendicular Fat, kg	−3 (4.0)	−1.8 (1.4)	−0.7 (1.0)	−1.5 (1.8)	0.1523	0.5187	0.0298 *
Trunk Fat, kg	−4.1 (2.4)	−2.9 (2.5)	−1.9 (2.7)	−1.8 (1.8)	0.5034	0.9746	0.0844
Android Fat, kg	−0.9 (0.5)	−0.6 (0.5)	−0.4 (0.4)	−0.4 (0.3)	0.3810	0.9198	0.0367 *
Gynoid Fat, kg	−1 (0.7)	−0.9 (0.7)	−0.4 (0.7)	−0.8 (0.6)	0.8396	0.2321	0.0395 *
Visceral Fat, kg	−0.4 (0.4)	−0.2 (0.2)	0.0 (0.3)	−0.1 (0.2)	0.1606	0.6264	0.0182 *
<b>Region Lean Mass—DXA</b>							
Total lean, kg	−0.3 (2.4)	−0.6 (2.0)	0.2 (1.6)	−1 (2.5)	0.7220	0.2214	0.5537
Trunk lean, kg	0.2 (1.3)	−0.3 (1.3)	0.2 (1.6)	−0.3 (1.3)	0.6762	0.4284	0.9850
Android lean, kg	−0.5 (1.2)	−0.3 (1.0)	0 (1.1)	−0.6 (1.3)	0.2428	0.2961	0.2210
Gynoid lean, kg	−0.2 (0.3)	−0.1 (0.2)	0 (0.1)	−0.1 (0.3)	0.2888	0.4527	0.0558
Appendicular lean, kg	−0.2 (0.4)	−0.2 (0.3)	−0.1 (0.4)	−0.1 (0.3)	0.7326	0.7984	0.3111
Data given as means (s.d.). IR=Insulin Resistant. IS=Insulin Sensitive. DXA=Dual X-ray-Absorptiometry. Paired contrasts adjusted for sex (M/W) and race (EA/AA). * p < 0.05.							

Within-group contrasts showed that insulin-sensitive and insulin-resistant participants lost similar amounts of total body and central fat mass and lean mass, regardless of diet (Figure 2A). Insulin-resistant participants on the LCHF diet had a greater increase in high density lipoprotein (HDL) than insulin-sensitive participants on the same diet ( $p < 0.05$ ) (Table 3).

#### 4. Discussion

The goal of this study was to determine whether prescribing a low carbohydrate high fat diet or a low fat low-calorie diet would result in greater loss of total body and central fat mass, less loss of lean mass among middle-aged adults with overweight and obesity. We also aimed to determine whether insulin resistance status would affect response to the intervention.

The main finding of this study was that compared to the LF diets, the LCHF diet prescription elicited a greater reduction in central fat mass. After the 15-week intervention period, we observed a greater reduction in android and visceral fat in the LCHF group, even though both groups lost similar amounts of weight and total body fat mass. These findings extend previous observations from our group, which showed that carbohydrate restriction yields greater loss of intra-abdominal fat among adults with overweight or obesity and women with polycystic ovary syndrome (PCOS) [7,9]. Together, these data suggest that the LCHF diet facilitates mobilization of fatty acids specifically from central and visceral depots, which may alleviate risk for age-related cardiometabolic disease in middle-aged adults [27].

The mechanism for the preferential loss of central fat with the LCHF diet is not fully understood. However, the results of this study align with the theory that fatty acids from the visceral depot have a higher turnover rate, and are generally mobilized first during negative energy balance, which may be amplified by the reduction in insulin secretion with a LCHF diet [28]. Further, lower insulin secretion would permit greater oxidation of fatty acids as a fuel, and reduce stimulation of triglyceride uptake in adipose tissue (re-esterification) [29]. In contrast, LF (high carbohydrate) diets retain greater insulin secretion during negative energy balance, and in some studies result in loss of greater lean body mass [30]. It is possible that the higher insulin with the LF diet results in greater use of glucose and amino acids for fuel, resulting in greater re-esterification of fatty acids into adipose tissue triglyceride stores. “The higher glucagon to insulin ratio observed with reduced carbohydrate diets [31] may also play a role in redistribution of energy from central fat depots [32].

We found that total body and appendicular lean mass were preserved in both groups. However, the LCHF group lost a small but statistically significant amount of central lean mass. In this population, weight loss prescriptions should avoid excess lean mass loss due to increased risk for sarcopenia and sarcopenic obesity, which are defined by excessive loss of total body or appendicular mass [33]. Since both total and appendicular lean mass were preserved in both groups, these findings suggest that there is no greater risk associated with lean mass loss from a short-term intervention on either a LF or LCHF diet.

Multiple studies have shown that serum measures that are associated with metabolic risk markedly improve with weight loss regardless of diet [5,34–38]. In this study, although both groups lost weight, those prescribed to the LCHF diet had a significant improvement in insulin resistance, whereas those prescribed to the LF diet showed worse insulin resistance. Likewise, the LCHF group showed a significant decrease in triglycerides, whereas the LF had a slight and non-significant decrease. Although the difference between groups did not reach statistical significance for the change in HOMA-IR or triglycerides, these differences may be nonetheless clinically significant in individual patients.

Similar findings were reported in a recent meta-analysis of 23 randomized controlled trials that compared LCHF and LF diets. Hu et al. reported that LCHF diets result in a greater improvements in overall lipid metabolism measured by triglycerides, HDL, low-density lipoprotein (LDL), and total cholesterol [39]. Such improvements with carbohydrate restriction may result from a shift of intrahepatic metabolism away from insulin-stimulated triglyceride synthesis toward ketone body production [40]. Conversely, LF diets that are high in carbohydrates are well known to increase cholesterol and endogenous triglyceride production [41]. Hence, independent of weight loss, prescribing a LCHF diet may confer additional reduction in disease risk over a LF diet.

We found that changes in body composition were likely impacted by insulin resistance status. Insulin-resistant participants in the LCHF group lost more android, gynoid, and visceral fat and had greater improvements in HOMA-IR than those in the LF group. There was no difference in the effect of diet prescription for insulin-sensitive adults. Our results are consistent with previous evidence, showing that the insulin-resistant phenotype has a better response to low carbohydrate diets [42]. Hjorth et al. and Pittas et al., stratified their sample by insulin sensitivity phenotype and fasting insulin, respectively, and found

that total body weight loss differed according to phenotype [13,15]. This study adds that those with insulin resistance lose more central fat in response to a low carbohydrate diet than those on a low fat diet. These data suggest that prescribing a LCHF diet may confer additional advantage over a LF diet for middle-aged adults with insulin resistance.

A limitation of this study was that it used a diet choice model, rather than a randomized control model. It is well established that choosing a low-carbohydrate diet is more common among individuals with dietary habits and preferences that are more consistent with the LCHF diet. However, studies show that choosing one's diet does not influence weight loss, health outcomes, or adherence [43,44]. Second, the dropout rate in this study was 37%, which is within the normal range for diet interventions [45]. However, sensitivity analyses confirmed that bias was not introduced by attrition. It should be noted that factors such as genetics, and other variables not assessed, may have contributed to variation in the outcomes measured. Additionally, energy intake was not reported in this study. Therefore, the possibility that differences in calorie intake between the groups cannot be ruled out as a potential contributor to the observed changes in body composition. Lastly, this study had a small sample that was 82% women and 81% European American. Therefore, the results may not accurately reflect diet response among men or African Americans. The influence of sex and insulin resistance status on the response to a LCHF diet intervention should be evaluated in future studies. Nevertheless, the strengths of this study were its rigorous medical supervision and investigation of the diet-phenotype interactions. This study was conducted in a weight loss clinic, supporting the feasibility of achieving clinically meaningful improvements in metabolic health with a LCHF intervention in a clinic setting.

In summary, among middle-aged adults with overweightness and obesity, choosing a low carbohydrate-high fat diet prescription was associated with a greater central fat loss than the low-fat low-calorie diet, even though weight and total fat mass loss were comparable. Those with an insulin-resistant phenotype fared better on the low-carbohydrate-high-fat diet versus the lower fat diet for central fat loss, suggesting that evaluating patients for insulin resistance status at the time of presentation may be useful for determining the optimal diet prescription to reduce central adiposity in this population. Conversely, for those with an insulin-sensitive phenotype, diet choice did not affect outcomes, indicating that insulin sensitive patients may benefit from range of diet options. These observations suggest that LCHF diets may be a better weight loss approach for middle-aged adults with overweight and obesity, especially those with diminished insulin sensitivity.

**Supplementary Materials:** The following are available online at <https://www.mdpi.com/2072-643/13/2/475/s1>, Table S1: Self-Reported Medical History of Study Participants. Table S2: Self-Reported Medication Use of Study Participants.

**Author Contributions:** Conceptualization, V.G.B. and B.A.G.; Data curation, V.G.B. and M.S.; Formal analysis, V.G.B. and R.A.D.; Funding acquisition, B.A.G.; Investigation, V.G.B., T.S., and A.M.G.; Methodology, V.G.B.; Project administration, M.S.; Supervision, T.S. and B.A.G.; Visualization, V.G.B.; Writing—original draft, V.G.B.; Writing—review and editing, V.G.B., R.A.D., A.M.G., and B.A.G. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award number T32HL105349; the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under award numbers P30DK056336, P30DK079626, and P30DK079626; the National Center for Advancing Translational Sciences under award number U54TR002731; and the National Institute of General Medical Sciences under the award number 5R25GM086256-10. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of The University of Alabama at Birmingham (protocol code F140115008 and 02-05-2014).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

**Acknowledgments:** We must acknowledge the University of Alabama at Birmingham (UAB) Metabolism and Human Physiology Core Laboratories (P30 DK56336 and P30DK079626) Nutrition Obesity Research Center (T32HL105349), Diabetes Research Center (P30DK079626), Center for Clinical and Translational Science (U54TR002731) and the UAB Department of Nutrition Sciences.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Jura, M.; Kozak, L.P. Obesity and related consequences to ageing. *AGE* **2016**, *38*. [[CrossRef](#)]
2. Locher, J.L.; Goldsby, T.U.; Goss, A.M.; Kilgore, M.L.; Gower, B.; Ard, J.D. Calorie restriction in overweight older adults: Do benefits exceed potential risks? *Exp. Gerontol.* **2016**, *86*, 4–13. [[CrossRef](#)]
3. Hunter, G.R.; Gower, B.A.; Kane, B.L. Age Related Shift in Visceral Fat. *Int. J. Body Compos. Res.* **2010**, *8*, 103–108.
4. Brinkworth, G.D.; Wycherley, T.P.; Noakes, M.; Buckley, J.D.; Clifton, P.M. Long-term effects of a very-low-carbohydrate weight-loss diet and an isocaloric low-fat diet on bone health in obese adults. *Nutrition* **2016**, *32*, 1033–1036. [[CrossRef](#)]
5. Bravata, D.M.; Sanders, L.; Huang, J.; Krumholz, H.M.; Olkin, I.; Gardner, C.D.; Bravata, D.M. Efficacy and safety of low-carbohydrate diets: A systematic review. *JAMA* **2003**, *289*, 1837–1850. [[CrossRef](#)]
6. Buyken, A.E.; Mela, D.J.; Dussort, P.; Johnson, I.T.; Macdonald, I.A.; Stowell, J.D.; Brouns, F.J.P.H. Dietary carbohydrates: A review of international recommendations and the methods used to derive them. *Eur. J. Clin. Nutr.* **2018**, *72*, 1625–1643. [[CrossRef](#)]
7. Gower, B.A.; Goss, A.M. A Lower-Carbohydrate, Higher-Fat Diet Reduces Abdominal and Intermuscular Fat and Increases Insulin Sensitivity in Adults at Risk of Type 2 Diabetes. *J. Nutr.* **2015**, *145*, 177S–183S. [[CrossRef](#)]
8. Gardner, C.D.; Trepanowski, J.F.; Del Gobbo, L.C. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with genotype pattern or insulin secretion: The dietfits randomized clinical trial. *JAMA* **2018**, *319*, 667–679. [[CrossRef](#)]
9. Goss, A.M.; Goree, L.L.; Ellis, A.C.; Chandler-Laney, P.C.; Casazza, K.; Lockhart, M.E.; Gower, B.A. Effects of diet macronutrient composition on body composition and fat distribution during weight maintenance and weight loss. *Obesity* **2013**, *21*, 1139–1142. [[CrossRef](#)]
10. Goss, A.M.; Gower, B.; Soleymani, T.; Stewart, M.; Pendergrass, M.; Lockhart, M.; Krantz, O.; Dowla, S.; Bush, N.; Barry, V.G. Effects of weight loss during a very low carbohydrate diet on specific adipose tissue depots and insulin sensitivity in older adults with obesity: A randomized clinical trial. *Nutr. Metab.* **2020**, *17*, 1–12.
11. Lee, J.-K.; Wu, C.-K.; Lin, L.-Y.; Cheng, C.-L.; Lin, J.-W.; Hwang, J.-J.; Chiang, F.-T. Insulin resistance in the middle-aged women with “Tigerish Back and Bearish Waist”. *Diabetes Res. Clin. Pract.* **2010**, *90*, e85–e87. [[CrossRef](#)]
12. Piché, M.-E.; Poirier, P.; Lemieux, I.; Després, J.-P. Overview of Epidemiology and Contribution of Obesity and Body Fat Distribution to Cardiovascular Disease: An Update. *Prog. Cardiovasc. Dis.* **2018**. [[CrossRef](#)]
13. Hjorth, M.F.; Ritz, C.; Blaak, E.E.; Saris, W.H.; Langin, D.; Poulsen, S.K.; Larsen, T.M.; Sørensen, T.I.; Zohar, Y.; Astrup, A. Pretreatment fasting plasma glucose and insulin modify dietary weight loss success: Results from 3 randomized clinical trials. *Am. J. Clin. Nutr.* **2017**, *106*, 499–505. [[CrossRef](#)]
14. Ryan, A.S.; Ortmeyer, H.K.; Sorkin, J.D. Exercise with calorie restriction improves insulin sensitivity and glycogen synthase activity in obese postmenopausal women with impaired glucose tolerance. *Am. J. Physiol. Endocrinol. Metab.* **2012**, *302*, E145–E152. [[CrossRef](#)]
15. Pittas, A.G.; Das, S.K.; Hajduk, C.L.; Golden, J.; Saltzman, E.; Stark, P.C.; Greenberg, A.S.; Roberts, S.B. A Low-Glycemic Load Diet Facilitates Greater Weight Loss in Overweight Adults With High Insulin Secretion but Not in Overweight Adults With Low Insulin Secretion in the CALERIE Trial. *Diabetes Care* **2005**, *28*, 2939–2941. [[CrossRef](#)]
16. Waters, D.L.; Ward, A.L.; Villareal, D.T. Weight loss in obese adults 65years and older: A review of the controversy. *Exp. Gerontol.* **2013**, *48*, 1054–1061. [[CrossRef](#)]
17. Schulz, K.F.; Altman, D.G.; Moher, D. CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMC Med.* **2010**, *8*, 18.
18. Goran, M.I.; Poehlman, E.T. Total energy expenditure and energy requirements in healthy elderly persons. *Metabolism* **1992**, *41*, 744–753. [[CrossRef](#)]
19. Stults-Kolehmainen, M.A.; Stanforth, P.R.; Bartholomew, J.B.; Lu, T.; Abolt, C.J.; Sinha, R. DXA estimates of fat in abdominal, trunk and hip regions varies by ethnicity in men. *Nutr. Diabetes* **2013**, *3*, e64. [[CrossRef](#)]
20. Micklesfield, L.K.; Goedecke, J.H.; Punyanitya, M.; Wilson, K.E.; Kelly, T.L. Dual-Energy X-Ray Performs as Well as Clinical Computed Tomography for the Measurement of Visceral Fat. *Obesity* **2012**, *20*, 1109–1114. [[CrossRef](#)]
21. Hind, K.; Oldroyd, B. In-vivo precision of the GE Lunar iDXA densitometer for the measurement of appendicular and trunk lean and fat mass. *Eur. J. Clin. Nutr.* **2013**, *67*, 1331–1333. [[CrossRef](#)]
22. Hind, K.; Oldroyd, B.; Truscott, J.G. In vivo precision of the GE Lunar iDXA densitometer for the measurement of total body composition and fat distribution in adults. *Eur. J. Clin. Nutr.* **2011**, *65*, 140–142. [[CrossRef](#)]

23. Kaul, S.; Rothney, M.P.; Peters, D.M.; Wacker, W.K.; Davis, C.E.; Shapiro, M.D.; Ergun, D.L. Dual-Energy X-Ray Absorptiometry for Quantification of Visceral Fat. *Obesity* **2012**, *20*, 1313–1318. [[CrossRef](#)]
24. Wallace, T.M.; Matthews, D.R. The assessment of insulin resistance in man. *Diabet. Med.* **2002**, *19*, 527–534. [[CrossRef](#)]
25. Qu, H.-Q.; Li, Q.; Rentfro, A.R.; Fisher-Hoch, S.P.; McCormick, J.B. The Definition of Insulin Resistance Using HOMA-IR for Americans of Mexican Descent Using Machine Learning. *PLoS ONE* **2011**, *6*, e21041. [[CrossRef](#)]
26. Association, A.D. Glycemic Targets. *Diabetes Care* **2017**, *40*, S48–S56. [[CrossRef](#)]
27. Freedland, E.S. Role of a critical visceral adipose tissue threshold (CVATT) in metabolic syndrome: Implications for controlling dietary carbohydrates: A review. *Nutr. Metab.* **2004**, *1*, 1–12. [[CrossRef](#)]
28. Magkos, F.; Fraterrigo, G.; Yoshino, J.; Luecking, C.; Kirbach, K.; Kelly, S.C.; De Las Fuentes, L.; He, S.; Okunade, A.L.; Patterson, B.W. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. *Cell Metab.* **2016**, *23*, 591–601.
29. Feinman, R.D.; Pogozelski, W.K.; Astrup, A.; Bernstein, R.K.; Fine, E.J.; Westman, E.C.; Accurso, A.; Frassetto, L.; Gower, B.A.; McFarlane, S.I.; et al. Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base. *Nutrition* **2015**, *31*, 1–13. [[CrossRef](#)]
30. Willoughby, D.; Hewlings, S.; Kalman, D. Body Composition Changes in Weight Loss: Strategies and Supplementation for Maintaining Lean Body Mass, a Brief Review. *Nutrients* **2018**, *10*, 1876. [[CrossRef](#)]
31. Walsh, C.O.; Ebbeling, C.B.; Swain, J.F.; Markowitz, R.L.; Feldman, H.A.; Ludwig, D.S. Effects of diet composition on postprandial energy availability during weight loss maintenance. *PLoS ONE* **2013**, *8*, e58172.
32. Scott, R.V.; Bloom, S.R. Problem or solution: The strange story of glucagon. *Peptides* **2018**, *100*, 36–41. [[CrossRef](#)]
33. Iannuzzi-Sucich, M.; Prestwood, K.M.; Kenny, A.M. Prevalence of Sarcopenia and Predictors of Skeletal Muscle Mass in Healthy, Older Men and Women. *J. Gerontol. Ser. A Biol. Sci. Med Sci.* **2002**, *57*, M772–M777. [[CrossRef](#)]
34. Foster, M.T.; Pagliassotti, M.J. Metabolic alterations following visceral fat removal and expansion: Beyond anatomic location. *Adipocyte* **2012**, *1*, 192–199. [[CrossRef](#)]
35. Schoeller, D.A.; Buchholz, A.C. Energetics of obesity and weight control: Does diet composition matter? *J. Am. Diet. Assoc.* **2005**, *105*, S24–S28. [[CrossRef](#)]
36. Ruth, M.R.; Port, A.M.; Shah, M.; Bourland, A.C.; Istfan, N.W.; Nelson, K.P.; Gokce, N.; Apovian, C.M. Consuming a hypocaloric high fat low carbohydrate diet for 12 weeks lowers C-reactive protein, and raises serum adiponectin and high density lipoprotein-cholesterol in obese subjects. *Metabolism* **2013**, *62*, 1779–1787. [[CrossRef](#)]
37. Tighe, P.; Duthie, G.; Vaughan, N.; Brittenden, J.; Simpson, W.G.; Duthie, S.; Mutch, W.; Wahle, K.; Horgan, G.; Thies, F. Effect of increased consumption of whole-grain foods on blood pressure and other cardiovascular risk markers in healthy middle-aged persons: A randomized controlled trial. *Am. J. Clin. Nutr.* **2010**, *92*, 733–740. [[CrossRef](#)]
38. Volek, J.S.; Sharman, M.J.; Gomez, A.L.; DiPasquale, C.; Roti, M.; Pumerantz, A.; Kraemer, W.J. Comparison of a very low-carbohydrate and low-fat diet on fasting lipids, LDL subclasses, insulin resistance, and postprandial lipemic responses in overweight women. *J. Am. Coll. Nutr.* **2004**, *23*, 177–184.
39. Hu, T.; Mills, K.T.; Yao, L.; Demanelis, K.; Eloustaz, M.; Yancy Jr, W.S.; Kelly, T.N.; He, J.; Bazzano, L.A. Effects of Low-Carbohydrate Diets Versus Low-Fat Diets on Metabolic Risk Factors: A Meta-Analysis of Randomized Controlled Clinical Trials. *Am. J. Epidemiol.* **2012**, *176*, S44–S54.
40. Farquhar, J.W.; Frank, A.; Gross, R.C.; Reaven, G.M. Glucose, insulin, and triglyceride responses to high and low carbohydrate diets in man. *J. Clin. Investig.* **1966**, *45*, 1648–1656. [[CrossRef](#)]
41. Parks, E.J.; Krauss, R.M.; Christiansen, M.P.; Neese, R.A.; Hellerstein, M.K. Effects of a low-fat, high-carbohydrate diet on VLDL-triglyceride assembly, production, and clearance. *J. Clin. Investig.* **1999**, *104*, 1087–1096. [[CrossRef](#)]
42. Volek, J.S.; Fernandez, M.L.; Feinman, R.D.; Phinney, S.D. Dietary carbohydrate restriction induces a unique metabolic state positively affecting atherogenic dyslipidemia, fatty acid partitioning, and metabolic syndrome. *Prog. Lipid Res.* **2008**, *47*, 307–318.
43. Yancy, W.S.; Mayer, S.B.; Coffman, C.J.; Smith, V.A.; Kolotkin, R.L.; Geiselman, P.J.; McVay, M.A.; Oddone, E.Z.; Voils, C.I. Effect of Allowing Choice of Diet on Weight Loss. A Randomized Trial. *Ann. Intern. Med.* **2015**, *162*, 805–814. [[CrossRef](#)]
44. McVay, M.A.; Voils, C.I.; Coffman, C.J.; Geiselman, P.J.; Kolotkin, R.L.; Mayer, S.B.; Smith, V.A.; Gaillard, L.; Turner, M.J.; Yancy, W.S. Factors associated with choice of a low-fat or low-carbohydrate diet during a behavioral weight loss intervention. *Appetite* **2014**, *83*, 117–124. [[CrossRef](#)]
45. Dalle Grave, R.; Calugi, S.; Compare, A.; El Ghoch, M.; Petroni, M.L.; Tomasi, F.; Mazzali, G.; Marchesini, G. Weight Loss Expectations and Attrition in Treatment-Seeking Obese Women. *Obes. Facts* **2015**, *8*, 311–318. [[CrossRef](#)]

## ORIGINAL ARTICLE

# A Randomized Trial of a Low-Carbohydrate Diet for Obesity

Gary D. Foster, Ph.D., Holly R. Wyatt, M.D., James O. Hill, Ph.D.,  
 Brian G. McGuckin, Ed.M., Carrie Brill, B.S., B. Selma Mohammed, M.D., Ph.D.,  
 Philippe O. Szapary, M.D., Daniel J. Rader, M.D., Joel S. Edman, D.Sc.,  
 and Samuel Klein, M.D.

---

## ABSTRACT

---

### BACKGROUND

From the University of Pennsylvania School of Medicine, Philadelphia (G.D.F., B.G.M., P.O.S., D.J.R.); University of Colorado Health Sciences Center, Denver (H.R.W., J.O.H., C.B.); Washington University School of Medicine, St. Louis (B.S.M., S.K.); and Thomas Jefferson University, Philadelphia (J.S.E.). Address reprint requests to Dr. Foster at the University of Pennsylvania, 3535 Market St, Suite 3027, Philadelphia, PA 19104-3309, or at [fosterg@mail.med.upenn.edu](mailto:fosterg@mail.med.upenn.edu).

N Engl J Med 2003;348:2082-90.  
 Copyright © 2003 Massachusetts Medical Society.

### METHODS

We conducted a one-year, multicenter, controlled trial involving 63 obese men and women who were randomly assigned to either a low-carbohydrate, high-protein, high-fat diet or a low-calorie, high-carbohydrate, low-fat (conventional) diet. Professional contact was minimal to replicate the approach used by most dieters.

### RESULTS

Subjects on the low-carbohydrate diet had lost more weight than subjects on the conventional diet at 3 months (mean [ $\pm$ SD],  $-6.8 \pm 5.0$  vs.  $-2.7 \pm 3.7$  percent of body weight;  $P=0.001$ ) and 6 months ( $-7.0 \pm 6.5$  vs.  $-3.2 \pm 5.6$  percent of body weight,  $P=0.02$ ), but the difference at 12 months was not significant ( $-4.4 \pm 6.7$  vs.  $-2.5 \pm 6.3$  percent of body weight,  $P=0.26$ ). After three months, no significant differences were found between the groups in total or low-density lipoprotein cholesterol concentrations. The increase in high-density lipoprotein cholesterol concentrations and the decrease in triglyceride concentrations were greater among subjects on the low-carbohydrate diet than among those on the conventional diet throughout most of the study. Both diets significantly decreased diastolic blood pressure and the insulin response to an oral glucose load.

### CONCLUSIONS

The low-carbohydrate diet produced a greater weight loss (absolute difference, approximately 4 percent) than did the conventional diet for the first six months, but the differences were not significant at one year. The low-carbohydrate diet was associated with a greater improvement in some risk factors for coronary heart disease. Adherence was poor and attrition was high in both groups. Longer and larger studies are required to determine the long-term safety and efficacy of low-carbohydrate, high-protein, high-fat diets.

**A**T ANY GIVEN TIME, APPROXIMATELY 45 percent of women and 30 percent of men in the United States are trying to lose weight.<sup>1</sup> Despite these efforts, the prevalence of obesity has doubled in the past 20 years<sup>2</sup> and has become a major public health problem.<sup>3</sup> The conventional dietary approach to weight management, recommended by the leading research and medical societies,<sup>4-7</sup> is a high-carbohydrate, low-fat, energy-deficit diet. Low-carbohydrate, high-protein, high-fat diets have become increasingly popular, and many best-selling diet books have promoted this approach.<sup>8,9</sup> The Atkins diet, originally published in 1973 and again in 1992 and 2002, may be the most popular of these diets. More than 10 million copies of Atkins's diet book have been sold,<sup>10</sup> and four times as many dieters have read one of the Atkins books as have read any other diet book.<sup>11</sup>

Despite its longevity and popularity, no randomized trials evaluating the efficacy of the Atkins diet have been published.<sup>12,13</sup> Data from short-term, uncontrolled studies indicate that the Atkins diet induces weight losses of 8.3 percent after 8 weeks<sup>14</sup> and 10.3 percent after 24 weeks.<sup>15</sup>

We conducted a one-year, multicenter, randomized, controlled trial to evaluate the effect of the low-carbohydrate, high-protein, high-fat Atkins diet on weight loss and risk factors for coronary heart disease in obese persons. The subjects were randomly assigned to follow either a low-carbohydrate, high-protein, high-fat Atkins diet or a high-carbohydrate, low-fat, energy-deficit conventional diet. Professional contact was minimal, so as to approximate the approach used by most dieters.

## METHODS

### SUBJECTS

A total of 63 persons (43 women and 20 men) participated in the study (Table 1). All subjects completed a comprehensive medical examination and routine blood tests. Potential subjects were excluded if they had clinically significant illnesses, including type 2 diabetes; were taking lipid-lowering medications; were pregnant or lactating; or were taking medications that affect body weight. All subjects provided written informed consent, and the protocol was approved by the institutional review boards of the participating institutions.

### STUDY DESIGN

The subjects were randomly assigned at each site, with use of a random-number generator, to follow

either the low-carbohydrate diet or the conventional diet. Subjects in both groups were instructed to take a daily multivitamin supplement and met with a registered dietitian for 15 to 30 minutes at 3, 6, and 12 months to review dietary issues.

### Low-Carbohydrate Diet

The 33 subjects who were assigned to the low-carbohydrate, high-protein, high-fat diet met individually with a registered dietitian before beginning the program to review the central features of the diet (available as Supplementary Appendix 1 with the full text of this article at <http://www.nejm.org>), which involves limiting carbohydrate intake without restricting consumption of fat and protein. For the first two weeks, carbohydrate intake is limited

**Table 1.** Base-Line Characteristics of the Subjects.\*

Characteristic	Low-Carbohydrate Diet (N=33)	Conventional Diet (N=30)
Sex (no. of subjects)		
Male	12	8
Female	21	22
Race or ethnic group (no. of subjects)†		
White	26	22
Black	4	8
Hispanic	3	0
Age (yr)	44.0±9.4	44.2±7.0
Body-mass index‡	33.9±3.8	34.4±3.1
Weight (kg)	98.7±19.5	98.3±16.4
Systolic blood pressure (mm Hg)	120.5±11.0	123.3±14.1
Diastolic blood pressure (mm Hg)	74.6±8.5	77.6±10.8
Triglycerides (mg/dl)	131.1±113.8	122.6±82.6
Cholesterol (mg/dl)		
Total	200.5±33.5	193.7±32.1
Low-density lipoprotein	129.5±30.0	119.8±30.0
High-density lipoprotein	46.8±11.2	49.4±12.5
Area under the curve		
Glucose (mg/dl/2 hr)	15,649.7±2956.3	15,540.2±2623.8
Insulin (μU/ml/2 hr)	8776.7±5072.5	10,025.7±5845.5
Insulin sensitivity§	0.35±0.05	0.34±0.04

\* Plus-minus values are means ±SD. There were no significant differences between the two groups. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

† The race or ethnic group was assigned by the subjects themselves.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Insulin sensitivity was calculated according to the quantitative insulin-sensitivity check index.<sup>16</sup>

**Table 2.** Percent Changes in Weight, Blood Pressure, Serum Lipoprotein Concentrations, and Oral Glucose Tolerance in an Analysis in Which Base-Line Values Were Carried Forward in the Case of Missing Data.\*

Variable	Low-Carbohydrate Diet (N=33)	Conventional Diet (N=30)	P Value†
percent change			
Weight			
Mo 3	-6.8±5.0‡	-2.7±3.7‡	0.001
Mo 6	-7.0±6.5‡	-3.2±5.6‡	0.02
Mo 12	-4.4±6.7‡	-2.5±6.3‡	0.26
Systolic blood pressure			
Mo 3	-2.6±11.2	-0.6±11.9	0.59
Mo 6	-2.3±11.7	1.0±12.2	0.28
Mo 12	-1.0±9.4	1.7±11.8	0.43
Diastolic blood pressure			
Mo 3	-3.0±13.4	-3.5±10.3‡	0.84
Mo 6	-4.0±12.7‡	-2.9±14.2	0.84
Mo 12	-3.7±12.4‡	-3.8±13.2	0.84
Triglycerides			
Mo 3	-18.7±25.7‡	1.1±34.6	0.01
Mo 6	15.0±29.4‡	-7.6±19.3‡	0.13
Mo 12	-17.0±23.0‡	0.7±37.7	0.04
Total cholesterol			
Mo 3	1.7±15.0	-5.4±10.1‡	0.03
Mo 6	2.4±9.3	-2.4±9.5	0.06
Mo 12	0.1±9.8	-2.9±8.0	0.27
Low-density lipoprotein cholesterol			
Mo 3	5.4±19.2	-7.4±16.6‡	0.007
Mo 6	2.7±12.8	-1.5±15.8	0.34
Mo 12	0.31±16.6	-3.1±12.0	0.52
High-density lipoprotein cholesterol			
Mo 3	9.6±19.1‡	1.4±16.1	0.04
Mo 6	14.7±20.5‡	2.5±12.0	0.007
Mo 12	11.0±19.4‡	1.6±11.1	0.04
Area under the glucose curve			
Mo 3	6.7±20.7	1.6±16.6	0.27
Mo 6	1.0±15.9	-0.8±12.2	0.80
Mo 12	3.2±16.2	1.2±10.1	0.80
Area under the insulin curve			
Mo 3	-14.1±27.6‡	-11.2±40.5‡	0.48
Mo 6	-14.7±25.7‡	-5.1±35.8	0.19
Mo 12	-11.2±24.7‡	-8.2±28.4‡	0.60
Insulin sensitivity§			
Mo 3	6.7±11.6‡	4.1±10.7	0.37
Mo 6	5.8±12.0‡	5.2±10.3‡	0.79
Mo 12	2.9±9.5	2.9±9.5	0.92

\* Plus-minus values are means ±SD.

† P values are for the differences between the two groups.

‡ P<0.05 for the difference from base line within the group.

§ Insulin sensitivity was calculated according to the quantitative insulin-sensitivity check index.<sup>16</sup>

to 20 g per day and is then gradually increased until a stable and desired weight is achieved. Each subject was given a copy of Dr. Atkins' New Diet Revolution,<sup>10</sup> which details the Atkins diet program. Subjects were instructed to read the book and follow the diet as described.

#### Conventional Diet

The 30 subjects who were assigned to the conventional diet also met with a registered dietitian before beginning the program to review the components of a high-carbohydrate, low-fat, low-calorie diet (1200 to 1500 kcal per day for women and 1500 to 1800 kcal per day for men, with approximately 60 percent of calories from carbohydrate, 25 percent from fat, and 15 percent from protein) and to receive instructions about calorie counting. Subjects were given a copy of The LEARN Program for Weight Management,<sup>17</sup> which provides 16 lessons covering various aspects of weight control. The nutritional information in the manual was consistent with the dietary recommendations provided by the study dietitian and with the Department of Agriculture Food Guide Pyramid.<sup>18</sup> Subjects were instructed to read the manual and follow the program as described.

#### OUTCOMES

Body weight was measured with the use of calibrated scales (Detecto 6800, Cardinal) while the subjects were wearing light clothing and no shoes at base line and at weeks 2, 4, 8, 12, 16, 20, 26, 34, 42, and 52. Blood pressure and urinary ketones were also assessed at base line and at weeks 2, 4, 8, 12, 16, 20, 26, 34, 42, and 52. Blood samples were obtained after subjects fasted overnight at base line and at 3, 6, and 12 months to determine serum lipoprotein concentrations. An oral glucose-tolerance test was performed at base line and at 3, 6, and 12 months. After subjects fasted overnight, blood samples were obtained for the measurement of plasma glucose and insulin concentrations before and 30, 60, 90, and 120 minutes after the oral administration of a 75-g glucose load. In addition, insulin sensitivity, based on fasting plasma glucose and insulin concentrations, was assessed with the use of quantitative insulin-sensitivity check index<sup>16</sup>:  $1 \div [(\log \text{fasting serum insulin level, in microunits per milliliter}) + (\log \text{fasting glucose level, in milligrams per deciliter})]$ .

#### ANALYSES OF SAMPLES

Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations

were assayed according to procedures recommended by the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute.<sup>19</sup> The low-density lipoprotein (LDL) cholesterol concentration was calculated according to the Friedewald formula<sup>20</sup> in all but one subject, who had a triglyceride concentration greater than 400 mg per deciliter (4.52 mmol per liter). Plasma insulin was measured by radioimmunoassay, and plasma glucose by a glucose oxidase autoanalyzer (Yellow Springs Instruments). The area under the curve (AUC) for the plasma glucose concentration and for the insulin concentration was calculated.<sup>21</sup> Urinary ketone concentrations were measured with dipsticks (Ketostix 2880, Bayer) and characterized dichotomously as negative (0 mg per deciliter) or positive (5 to 100 mg per deciliter).

#### STATISTICAL ANALYSIS

Analysis of variance revealed no effects of the research site on weight loss or attrition at 3, 6, or 12 months, so the data on all the subjects were analyzed together. A t-test for independent samples was used to assess differences in base-line variables between the groups. Two sets of analyses were conducted. The primary analysis was a repeated-measures analysis of variance in which the base-line value was carried forward in the case of missing data. In a secondary analysis, an analysis of covariance (in which initial weights were covariates) was used to examine changes in weight from base line to the end of the study, for those who completed the study, or at the time of the last follow-up visit, for those who did not complete the study. A chi-square analysis was performed to determine differences between groups in categorical variables, and correlations with categorical variables were assessed with Spearman's rho coefficient. Triglyceride values were not normally distributed, so the log-transformed values were analyzed. Results are presented as percent changes to facilitate clinical interpretation, although all analyses involved absolute values and were conducted with the use of SPSS software (version 11.0).<sup>22</sup>

#### RESULTS

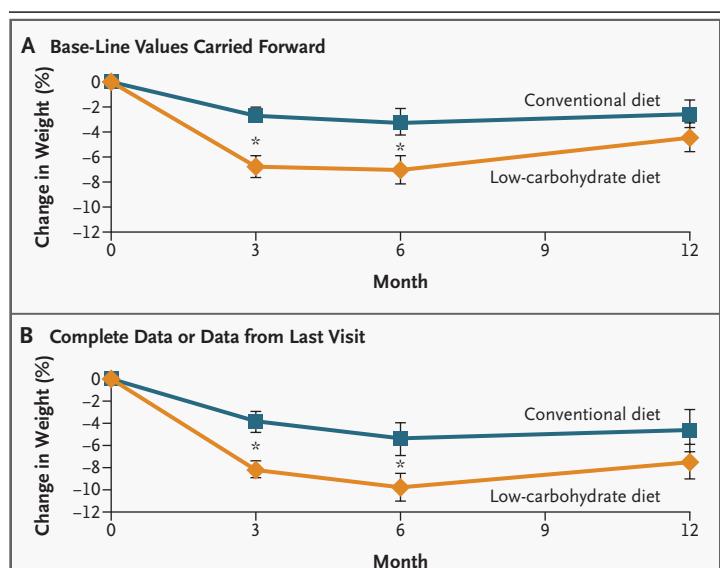
##### WEIGHT

In the analysis in which base-line values were carried forward in the case of missing values, the group on the low-carbohydrate diet had lost significantly more weight than the group on the conventional

diet at 3 months ( $P=0.001$ ) and 6 months ( $P=0.02$ ), but the difference in weight loss was not statistically significant at 12 months ( $P=0.26$ ) (Table 2 and Fig. 1A).

##### ATTRITION

A total of 49 subjects completed 3 months of the study (28 on the low-carbohydrate diet and 21 on the conventional diet), 42 subjects completed 6 months (24 on the low-carbohydrate diet and 18 on the conventional diet), and 37 subjects completed 12 months (20 on the low-carbohydrate diet and 17 on the conventional diet). The percentage of subjects who had dropped out of the study at 3, 6, and 12 months was higher in the group following the conventional diet (30, 40, and 43 percent, respectively) than in the group following the low-carbohydrate diet (15, 27, and 39 percent, respectively), but these differences were not statistically significant. Overall, 59 percent of subjects completed the study, and 88 percent of those who completed the



**Figure 1.** Mean ( $\pm$ SE) Percent Change in Weight among Subjects on the Low-Carbohydrate Diet and Those on the Conventional (Low-Calorie, High-Carbohydrate) Diet, According to an Analysis in Which Base-Line Values Were Carried Forward in the Case of Missing Values (Panel A) or an Analysis That Included Data on Subjects Who Completed the Study and Data Obtained at the Time of the Last Follow-up Visit for Those Who Did Not Complete the Study (Panel B).

In Panel B, the low-carbohydrate group had 28 subjects at 3 months, 24 subjects at 6 months, and 20 subjects at 12 months and the conventional-diet group had 21 subjects at 3 months, 18 subjects at 6 months, and 17 subjects at 12 months. Asterisks indicate a significant difference ( $P<0.05$ ) between the groups.

**Table 3.** Percent Changes in Weight, Blood Pressure, Serum Lipoproteins, and Oral Glucose Tolerance in an Analysis That Included Data on Subjects Who Completed the Study and Data Obtained at the Time of the Last Follow-up Visit for Those Who Did Not Complete the Study.\*

Variable	Low-Carbohydrate Diet	Conventional Diet	P Value†
	percent change		
Weight			
Mo 3	-8.1±4.4‡	-3.8±3.9‡	0.002
Mo 6	-9.7±5.7‡	-5.3±6.4‡	0.03
Mo 12	-7.3±7.3‡	-4.5±7.9‡	0.27
Systolic blood pressure			
Mo 3	-3.1±12.1	-0.8±14.3	0.69
Mo 6	-3.2±12.7	1.6±15.9	0.36
Mo 12	-1.6±12.2	2.9±15.8	0.44
Diastolic blood pressure			
Mo 3	-3.5±14.5	-5.1±12.1‡	0.65
Mo 6	-5.5±14.7‡	-4.9±18.3	0.95
Mo 12	-6.1±15.6‡	-6.7±17.2	0.76
Triglycerides			
Mo 3	-22.0±26.6‡	1.7±42.8	0.03
Mo 6	-20.6±32.8‡	-13.3±24.3‡	0.27
Mo 12	-28.1±23.6‡	1.4±52.5	0.04
Total cholesterol			
Mo 3	2.0±16.3	-8.2±11.5‡	0.02
Mo 6	3.3±10.9	-4.2±12.5	0.06
Mo 12	0.2±12.7	-5.5±10.4	0.23
Low-density lipoprotein cholesterol			
Mo 3	6.2±20.4	-11.1±19.4‡	0.005
Mo 6	3.6±14.8	-2.7±21.1	0.35
Mo 12	0.5±21.2	-5.8±16.1	0.47
High-density lipoprotein cholesterol			
Mo 3	11.4±20.3‡	2.1±19.8	0.07
Mo 6	20.2±21.7‡	4.4±15.8	0.02
Mo 12	18.2±22.4‡	3.1±15.2	0.04
Area under the glucose curve			
Mo 3	7.9±22.3	2.3±19.9	0.33
Mo 6	1.4±18.7	-1.4±16.5	0.76
Mo 12	5.3±20.8	2.4±14.4	0.87
Area under the insulin curve			
Mo 3	-16.7±29.3‡	-16.0±48.0‡	0.23
Mo 6	-20.2±28.4‡	-9.0±47.8	0.37
Mo 12	-18.4±29.8‡	-16.5±39.1‡	0.34
Insulin sensitivity§			
Mo 3	7.9±12.3‡	5.9±12.4	0.56
Mo 6	8.0±13.4‡	8.7±12.1‡	0.94
Mo 12	4.8±12.0	5.4±12.7	0.98

\* Plus-minus values are means ±SD. The low-carbohydrate group had 28 subjects at 3 months, 24 subjects at 6 months, and 20 subjects at 12 months. The conventional-diet group had 21 subjects at 3 months, 18 subjects at 6 months, and 17 subjects at 12 months.

† P values are for the differences between the two groups.

‡ P<0.05 for the difference from base line within the group.

§ Insulin sensitivity was calculated according to the quantitative insulin-sensitivity check index.<sup>16</sup>

six-month assessment completed the full study. When the analysis included data on subjects who completed the study and data obtained at the time of the last follow-up visit for those who did not complete the study, the pattern of weight loss was similar to that obtained when the base-line values were carried forward in the case of missing data. Subjects on the low-carbohydrate diet lost significantly more weight than the subjects on the conventional diet at 3 months ( $P=0.002$ ) and 6 months ( $P=0.03$ ), but the difference in weight loss was not statistically significant at 12 months ( $P=0.27$ ) (Table 3 and Fig. 1B).

#### URINARY KETONES

During the first three months, the percentage of patients who tested positive for urinary ketones was significantly greater in the group on the low-carbohydrate diet than in the group on the conventional diet (Fig. 2), but there were no significant differences between the groups after three months. There was no significant relation between weight loss and ketosis at any time during the study.

#### BLOOD PRESSURE

Systolic blood pressure did not change significantly in either group during the study (Tables 2 and 3). Diastolic pressure decreased in both groups, but there were no significant differences between groups.

#### ORAL GLUCOSE-TOLERANCE TEST

The area under the glucose curve did not change significantly in either group throughout the study. The area under the insulin curve decreased in both groups, but there were no significant differences between groups (Tables 2 and 3). There were no significant differences between groups in insulin sensitivity (assessed by the quantitative insulin-sensitivity check index<sup>16</sup>) throughout the study period. Both groups had significant increases in insulin sensitivity at six months, but the values were not significantly different from base line at one year (Tables 2 and 3).

#### SERUM LIPOPROTEINS

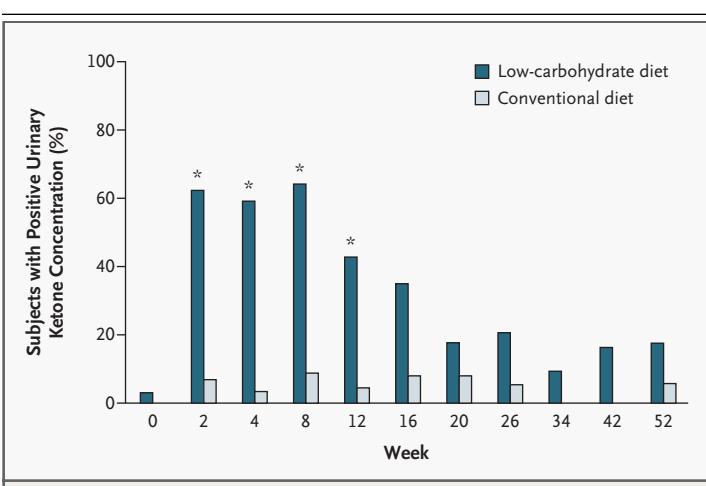
The effects of the diets on serum lipoproteins are shown in Tables 2 and 3 and Figure 3. There were no significant differences between groups in the total or LDL cholesterol concentration, except at month 3, when values were significantly lower in the group on the conventional diet than in the group on the low-carbohydrate diet. In contrast, the rela-

tive increase in HDL cholesterol concentrations and the relative decrease in triglyceride concentrations were greater in the group on the low-carbohydrate diet than in the group on the conventional diet throughout most of the study. The results of the analyses that included data on subjects who completed the study and data obtained at the time of the last follow-up visit for those who did not complete the study (Table 3) were nearly identical to the analyses in which base-line values were carried forward in the case of missing data (Table 2) with respect to blood pressure, insulin sensitivity, and serum lipoproteins.

## DISCUSSION

The results of this multicenter, randomized, controlled trial demonstrate that the low-carbohydrate, high-protein, high-fat Atkins diet produces greater weight loss (an absolute difference of approximately 4 percent) than a conventional high-carbohydrate, low-fat diet for up to six months, but that the differences do not persist at one year. The magnitude of weight loss at six months in the low-carbohydrate group approximates that achieved by standard behavioral<sup>23</sup> and pharmacologic<sup>24</sup> treatments. These weight losses are particularly noteworthy because the diet was implemented in a self-help format and subjects had little contact with health professionals. The lack of a statistically significant difference between the groups at one year is most likely due to greater weight regain in the low-carbohydrate group and the small sample size. These data suggest that long-term adherence to the low-carbohydrate Atkins diet may be difficult.

The difference in weight loss between the two groups in the first six months demonstrates an overall greater energy deficit in the low-carbohydrate group, despite unrestricted protein and fat intake in this group and instructions to restrict energy intake in the conventional-diet group. When the energy content of an energy-deficit diet is stable, macronutrient composition does not influence weight loss.<sup>25-28</sup> The mechanism responsible for the decreased energy intake induced by a low-carbohydrate diet with unrestricted protein and fat intake is not known but may be related to the monotony or simplicity of the diet, alterations in plasma or central satiety factors, or other factors that affect appetite and dietary adherence. Our data suggest that ketosis was unlikely to be responsible for the increased weight loss with the low-carbohydrate diet,



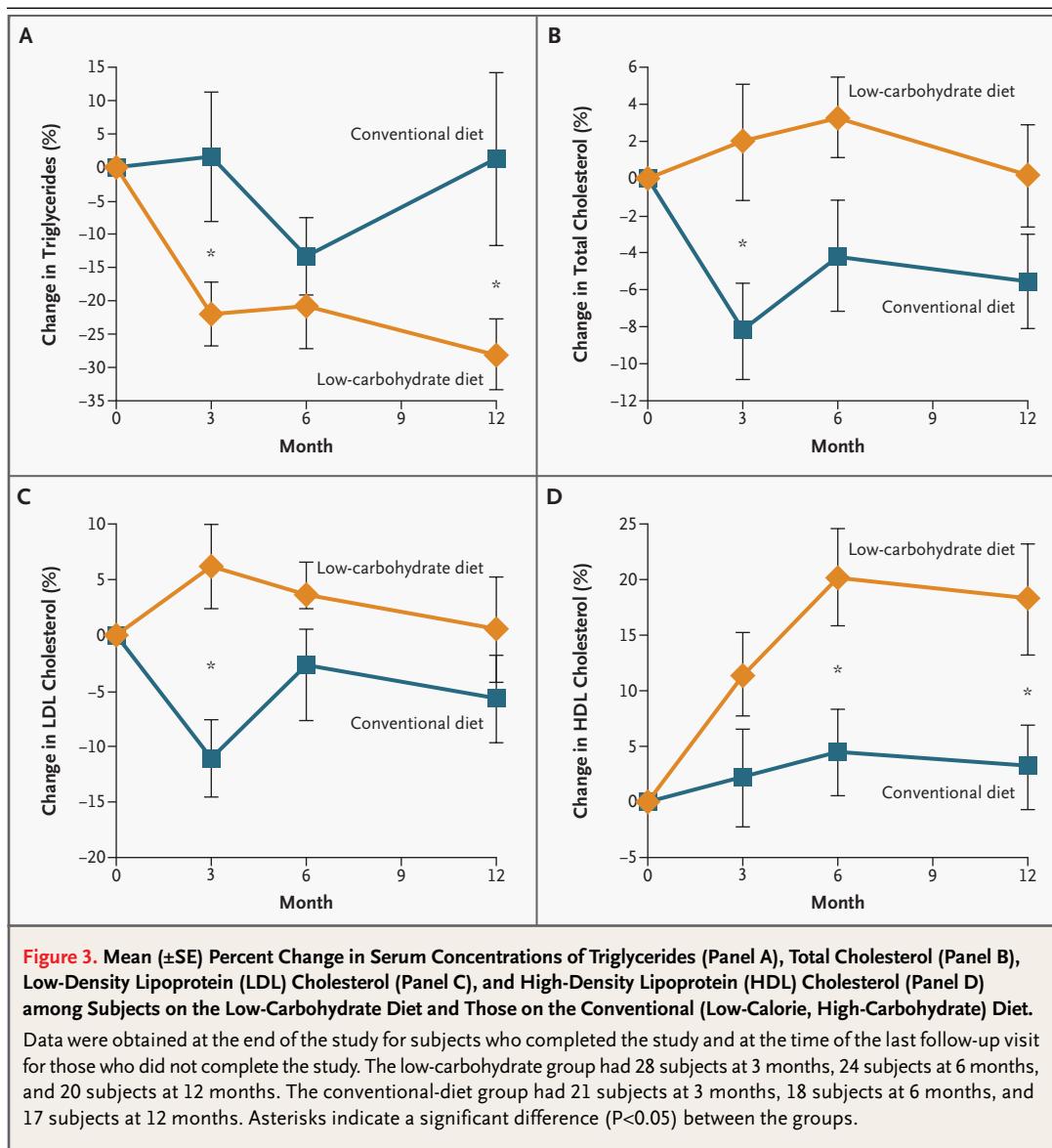
**Figure 2.** Percentage of Subjects with a Positive Urinary Ketone Concentration, According to Whether They Were on the Low-Carbohydrate Diet or the Conventional (Low-Calorie, High-Carbohydrate) Diet.

A positive urinary ketone concentration was defined as 5 to 100 mg per deciliter. Asterisks indicate a significant difference ( $P<0.003$ ) between the groups.

since we did not find any relation between the presence of urinary ketones and weight loss. Furthermore, urinary ketones were not present in most subjects on either diet after the first six months.

Although subjects with diabetes were excluded from our study, many — if not most — of our subjects, because of their obesity, were probably insulin-resistant with respect to glucose metabolism.<sup>29</sup> Treatment with either diet was associated with an improvement in insulin sensitivity as determined by an oral glucose-tolerance test; progressively less insulin was secreted to maintain the same blood glucose concentrations. These data do not demonstrate an effect of macronutrient composition, independent of weight loss, on insulin sensitivity in obese subjects without diabetes. However, the results of these metabolic studies should be interpreted with caution, given the study's relatively small sample size and the one-year duration. Additional studies in which more precise measures of insulin sensitivity are used are needed to evaluate this issue more carefully.

An important health concern of consuming unrestricted amounts of saturated fat is the potential to increase the LDL cholesterol concentration, which is an established risk factor for coronary heart disease. In fact, at three months, the LDL cholesterol concentration tended to increase in the subjects on the low-carbohydrate diet but decreased in the subjects on the conventional diet, so the difference be-



tween groups was significant. Over the long term, however, the LDL cholesterol concentration among subjects on the low-carbohydrate diet was similar to base-line values, and the changes in LDL cholesterol concentrations did not differ significantly between the groups. These data suggest that the increased weight loss associated with the low-carbohydrate diet may offset the adverse effect of saturated fat intake on serum LDL cholesterol concentrations. Nonetheless, weight loss with the low-carbohydrate diet was not associated with the decreases in LDL cholesterol usually observed with moderate weight loss.<sup>4,30</sup>

In contrast, the low-carbohydrate diet was associated with greater decreases in serum triglycerides and greater increases in HDL cholesterol than was the conventional diet, and the levels of both are also important risk factors for coronary heart disease.<sup>31-33</sup> The magnitude of these changes approximates that obtained with pharmacologic treatments, such as derivatives of fibric acid and niacin.<sup>31</sup> Although part of this benefit may be due to the greater weight loss with the low-carbohydrate diet, the changes are greater than those expected from a moderate weight loss alone.<sup>30</sup> Therefore, it is likely that the macronutrient composition of the diet

contributed to the improvement in the HDL cholesterol-triglyceride axis. High-carbohydrate, low-fat diets decrease HDL cholesterol concentrations and increase serum triglyceride concentrations,<sup>34-37</sup> whereas low-carbohydrate, high-fat diets decrease triglyceride concentrations<sup>16,27,37</sup> and increase HDL cholesterol concentrations.<sup>15</sup> Moreover, replacing dietary polyunsaturated or monounsaturated fat with carbohydrate is associated with an increased risk of coronary heart disease, as predicted by changes in triglyceride and HDL cholesterol concentrations.<sup>38</sup>

The overall effect of the low-carbohydrate diet in comparison with a conventional diet on the risk of coronary heart disease in our subjects is uncertain. As compared with the conventional diet, the low-carbohydrate diet was associated with a greater improvement in some risk factors for coronary heart disease (serum triglycerides and serum HDL cholesterol), but not others (blood pressure, insulin sensitivity, and serum LDL cholesterol). Moreover, the clinical significance of the favorable changes in the HDL cholesterol-triglyceride axis in the setting of a high fat intake is not clear. Additional, long-term studies are needed to determine whether increased serum HDL cholesterol concentrations and decreased serum triglyceride concentrations have the same effect on cardiovascular outcomes when one is consuming a diet high in saturated fat. It is also possible that the large amount of saturated fats and small amounts of fruits, vegetables, and fiber consumed during the low-carbohydrate diet can independently increase the risk of coronary heart disease.<sup>39,40</sup> Therefore, at the present time, there is not enough information to determine whether the beneficial effects of the Atkins diet outweigh its potential adverse effects on the risk of coronary heart disease in obese persons.

Our study has several limitations. The self-help nature of treatment, which is consistent with the way in which the low-carbohydrate diet is typically used, probably contributed to the attrition rate of 41 percent. This high rate of attrition underscores the difficulty of long-term compliance with either diet, when diet therapy is given with minimal supervision. More comprehensive behavioral treatment (e.g., weekly group meetings or self-monitoring) would probably have decreased attrition, increased adherence, and made possible a comparison with clinic-based treatments for obesity.<sup>23</sup> Our study was focused on weight and specific risk factors for coronary heart disease. We did not evaluate the effect of the low-carbohydrate diet on other important clinical end points, such as renal function, bone health, cardiovascular function, and exercise tolerance. Finally, our findings should not be generalized to overweight subjects or to obese subjects with serious obesity-related diseases, such as diabetes and hypercholesterolemia. Additional studies are needed in these populations to evaluate the safety and efficacy of low-carbohydrate, high-protein, high-fat diets.

Supported by grants from the National Institutes of Health (RR00036, RR00040, RR00051, AT1103, DK 37948, DK 56341, DK48520, DK42549, DK02703, and AT00058).

Dr. Foster reports having received consulting fees from Abbott Laboratories and HealthTech and lecture fees from Abbott Laboratories and Roche Laboratories. Dr. Wyatt reports having received consulting fees from Ortho-McNeil, USANA, and GlaxoSmithKline and lecture fees from Roche Laboratories, Abbott Laboratories, Slim-Fast, and Ortho-McNeil. Dr. Hill reports having received consulting fees from HealthTech, Johnson & Johnson, Procter & Gamble, Coca-Cola, and the International Life Sciences Institute; lecture fees from Abbott Laboratories, Roche Laboratories, and Kraft Foods; and grant support from M&M Mars, Procter & Gamble, and Abbott Laboratories. Dr. Szapary reports having received lecture fees from AstraZeneca and Kos Pharmaceuticals and grant support from AstraZeneca. Dr. Klein reports having received consulting fees from Roche Laboratories and HealthTech, lecture fees from Ortho-McNeil, and grants from GlaxoSmithKline and Regeneron.

#### REFERENCES

- Serdula MK, Mokdad AH, Williamson DF, Galuska DA, Mendlein JM, Heath GW. Prevalence of attempting weight loss and strategies for controlling weight. *JAMA* 1999; 282:1353-8.
- Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA* 2002; 288:1723-7.
- Department of Health and Human Services. The Surgeon General's call to action to prevent and decrease overweight and obesity. Washington, D.C.: Government Printing Office, 2001.
- Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults — the Evidence Report. *Obes Res* 1998;6:Suppl 2:51S-209S. [Erratum, *Obes Res* 1998;6:464.]
- Thomas PR, ed. Weighing the options: criteria for evaluating weight-management programs. Washington, D.C.: National Academy Press, 1995.
- Position of the American Dietetic Association: weight management. *J Am Diet Assoc* 1997;97:71-4.
- Krauss RM, Deckelbaum RJ, Ernst N, et al. Dietary guidelines for healthy American adults: a statement for health professionals from the National Committee, American Heart Association. *Circulation* 1996;94: 1795-800.
- Steward HL, Bethea MC, Andrews SS, Balart LA. Sugar busters! New York: Ballantine Publishing, 1995.
- Eades MR, Eades MD. Protein power. New York: Bantam Books, 1999.
- Atkins RC. Dr. Atkins' new diet revolution. Rev. ed. New York: Avon Books, 1998.
- The truth about dieting. Consumer Reports. June 2002:26-32.
- Freedman MR, King J, Kennedy E. Popular diets: a scientific review. *Obes Res* 2001;9:Suppl 1:1S-40S.
- Blackburn GL, Phillips JCC, Morreale S.

- Physician's guide to popular low-carbohydrate weight-loss diets. Cleve Clin J Med 2001;68:761, 765-6, 768-9, 773-4.
14. Larosa JC, Fry AG, Muesing R, Rosing DR. Effects of high-protein, low-carbohydrate dieting on plasma lipoproteins and body weight. J Am Diet Assoc 1980;77:264-70.
  15. Westman EC, Yancy WS, Edman JS, Tomlin KF, Perkins CE. Effect of 6-month adherence to a very low carbohydrate diet program. Am J Med 2002;113:30-6.
  16. Katz A, Nambi SS, Mather K, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000;85:2402-10.
  17. Brownell KD. The LEARN program for weight management 2000. Dallas: American Health Publishing, 2000.
  18. Food guide pyramid. Home and garden bulletin report 252. Washington, D.C.: Department of Agriculture, 1992.
  19. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. Clin Chem 1974;20:470-5.
  20. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein in plasma, without the use of preparative ultracentrifuge. Clin Chem 1972;18:499-502.
  21. Potteiger JA, Jacobsen DJ, Donnelly JE. A comparison of methods for analyzing glucose and insulin areas under the curve following nine months of exercise in overweight adults. Int J Obes Relat Metab Disord 2002;26:87-9.
  22. SPSS 11.0 for Windows. Chicago: SPSS, 2000.
  23. Wadden TA, Foster GD. Behavioral treatment of obesity. Med Clin North Am 2000;84:441-61.
  24. Yanovski SZ, Yanovski JA. Obesity. N Engl J Med 2002;346:591-602.
  25. Yang M-U, Van Itallie TB. Composition of weight lost during short-term weight reduction: metabolic responses of obese subjects to starvation and low-calorie ketogenic and nonketogenic diets. J Clin Invest 1976;58:722-30.
  26. Rabast U, Kasper H, Schonborn J. Comparative studies in obese subjects fed carbohydrate-restricted and high carbohydrate 1,000-calorie formula diets. Nutr Metab 1978;22:269-77.
  27. Golay A, Allaz AF, Morel Y, de Tonnac N, Tankova S, Reaven GM. Similar weight loss with low- or high-carbohydrate diets. Am J Clin Nutr 1996;63:174-8.
  28. Golay A, Eigenheer C, Morel Y, Kujawski P, Lehmann T, de Tonnac N. Weight loss with low or high carbohydrate diet? Int J Obes Relat Metab Disord 1996;20:1067-72.
  29. Ferrannini E, Natali A, Bell P, Cavallero Perin P, Lalic N, Mingrone G. Insulin resistance and hypersecretion in obesity. J Clin Invest 1997;100:1166-73.
  30. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoprotein: a meta-analysis. Am J Clin Nutr 1992;56:320-8.
  31. Szapary PO, Rader DJ. Pharmacological management of high triglycerides and low high-density lipoprotein cholesterol. Curr Opin Pharmacol 2001;1:113-20.
  32. Forrester JS. Triglycerides: risk factor or fellow traveler? Curr Opin Cardiol 2001;16:261-4.
  33. Boden WE. High-density lipoprotein cholesterol as an independent risk factor in cardiovascular disease: assessing the data from Framingham to the Veterans Affairs High-Density Lipoprotein Intervention Trial. Am J Cardiol 2000;86:19L-22L.
  34. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis of 27 trials. Arterioscler Thromb Vasc Biol 1992;12:911-9.
  35. Garg A, Grundy SM, Unger RH. Comparison of effects of high and low carbohydrate diets on plasma lipoproteins and insulin sensitivity in patients with mild NIDDM. Diabetes 1992;41:1278-85.
  36. Ornish D, Scherwitz LW, Billings JH, et al. Intensive lifestyle changes for reversal of coronary heart disease. JAMA 1998;280:2001-7. [Erratum, JAMA 1999;281:1380.]
  37. Lewis SB, Wallin JD, Kane JP, Gerich JE. Effect of diet composition on metabolic adaptations to hypocaloric nutrition: comparison of high carbohydrate and high fat isocaloric diets. Am J Clin Nutr 1977;30:160-70.
  38. Hu FB, Stampfer MJ, Manson JE, et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337:1491-9.
  39. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.
  40. Schaefer EJ. Lipoproteins, nutrition, and heart disease. Am J Clin Nutr 2002;75:191-212.

Copyright © 2003 Massachusetts Medical Society.

#### CLINICAL PROBLEM-SOLVING SERIES

The Journal welcomes submissions of manuscripts for the Clinical Problem-Solving series. This regular feature considers the step-by-step process of clinical decision making. For more information, please see <http://www.nejm.org/hfa/articles.asp>.

# Weight Loss on Low-Fat vs. Low-Carbohydrate Diets by Insulin Resistance Status Among Overweight Adults and Adults With Obesity: A Randomized Pilot Trial

Christopher D. Gardner<sup>1</sup>, Lisa C. Offringa<sup>1</sup>, Jennifer C. Hartle<sup>1</sup>, Kris Kapphahn<sup>2</sup>, and Rise Cherin<sup>1</sup>

**Objective:** To test for differential weight loss response to low-fat (LF) vs. low-carbohydrate (LC) diets by insulin resistance status with emphasis on overall quality of both diets.

**Methods:** Sixty-one adults, BMI 28-40 kg/m<sup>2</sup>, were randomized in a 2 × 2 design to LF or LC by insulin resistance status in this pilot study. Primary outcome was 6-month weight change. Participants were characterized as more insulin resistant (IR) or more insulin sensitive (IS) by median split of baseline insulin-area-under-the-curve from an oral glucose tolerance test. Intervention consisted of 14 one-hour class-based educational sessions.

**Results:** Baseline % carbohydrate:% fat:% protein was 44:38:18. At 6 months, the LF group reported 57:21:22 and the LC group reported 22:53:25 (IR and IS combined). Six-month weight loss (kg) was  $7.4 \pm 6.0$  (LF-IR),  $10.4 \pm 7.8$  (LF-IS),  $9.6 \pm 6.6$  (LC-IR), and  $8.6 \pm 5.6$  (LC-IS). No significant main effects were detected for weight loss by diet group or IR status; there was no significant diet × IR interaction. Significant differences in several secondary outcomes were observed.

**Conclusions:** Substantial weight loss was achieved overall, but a significant diet × IR status interaction was not observed. Opportunity to detect differential response may have been limited by the focus on high diet quality for both diet groups and sample size.

Obesity (2016) 24, 79–86. doi:10.1002/oby.21331

## Introduction

Obesity is related to increased risk of heart disease, stroke, type 2 diabetes, and some cancers (1). Individuals with moderate obesity with insulin resistance have a greater metabolic risk profile for these chronic diseases than those with greater insulin sensitivity, even at the same weight (2). Weight loss improves insulin sensitivity and lowers cardiovascular risk (3). However, most people find successful weight loss challenging. The weight loss diet traditionally recommended by health professionals has been a low-fat (LF), calorie-restricted diet (4), which may be particularly inappropriate for insulin resistant (IR) individuals, and has been challenged by proponents of alternative dietary strategies, particularly low-carbohydrate (LC) (5-7).

Several weight loss diet studies have examined whether differences in glucose and insulin dynamics (e.g., differential insulin secretion or insu-

lin resistance status) are a mediating factor for successful weight loss on LF vs. LC diets (8-12). These studies have consistently observed that overweight adults with higher insulin secretion or insulin resistance lose more weight on LC than LF diets. In contrast, lower insulin secretion or the more insulin sensitive (IS) individuals in these trials had more or comparable success with an LF diet. McClain et al. (10) observed that participants with higher baseline fasting insulin concentrations had lower adherence than participants with lower fasting insulin concentrations when assigned LF, even when unaware of their baseline fasting insulin status. Several proposed mechanisms support the plausibility of greater weight loss on an LC diet among IR individuals, including increased fatty acid uptake, inhibition of lipolysis, and effects on hunger, snacking, and energy intake (12-18).

The study objective was to conduct a pilot study continuing the research on the potential mediating effects of insulin resistance

<sup>1</sup> Stanford Prevention Research Center, Department of Medicine, Stanford University Medical School, Stanford, California, USA <sup>2</sup> Quantitative Sciences Unit, Department of Medicine, Stanford University Medical School, Stanford, CA. Correspondence: Christopher D. Gardner (cgardner@stanford.edu)

**Funding agencies:** Hass Avocado Board (to C.D.G.); by NIH (IRACDA Postdoctoral Fellowship to L.C.O.) grant 1 K12 GM088033; by an unrestricted grant from the Nutrilite Health Institute (to J.C.H.); and by Human Health Service grant M01-RR00070, General Clinical Research Centers, National Center for Research Resources, NIH.

**Disclosure:** The authors declare no conflict of interest.

**Author contributions:** C.D.G. and R.C. conceived and carried out the study. K.K., L.C.O., and J.C.H. analyzed the data. All authors contributed to writing the manuscript and had final approval of the submitted and published versions.

**Clinical trial registration:** Clinicaltrials.gov identifier NCT01661426.

Additional Supporting Information may be found in the online version of this article.

**Received:** 2 February 2015; **Accepted:** 3 August 2015; **Published online** 6 December 2015. doi:10.1002/oby.21331

status on weight loss responses to LF vs. LC diets. Particular emphasis was placed on maximizing the fat vs. carbohydrate differentials on the two diets and on overall nutritional quality.

## Methods

### Participants

Participants were recruited from the local community primarily through media advertisements. Premenopausal women and men aged 18–50 years were invited to enroll if BMI was 28–40 kg/m<sup>2</sup>, body weight was stable over the previous 2 months, and medications were stable for ≥3 months. Potential participants were excluded if they self-reported: hypertension (except for those stable on antihypertension medications), type 1 or 2 diabetes mellitus, heart, renal, or liver disease, cancer or active neoplasms, hyperthyroidism unless treated and under control, taking any medications known to affect weight/energy expenditure or blood lipids, smoking, alcohol intake ≥3 drinks/day, pregnancy, lactation, no menstruation for the previous 12 months, or plans to become pregnant within the next year. Race/ethnicity data were collected by self-report. All study participants provided written informed consent. The study was approved by the Stanford University Human Subjects Committee.

### Study design

The study employed a 2 × 2 design: LF vs. LC diets and more IR vs. more IS. We suggest the terms “insulin resistance” and “insulin sensitivity” here be interpreted cautiously as we used a proxy measure for this, rather than a direct measure (expanded discussion in Section 1 of Supporting Information). The method of determining relative insulin resistance was to calculate an area under the curve of insulin concentrations (AUC-INS) from four blood samples taken during an oral glucose tolerance test (OGTT) (time 0, 30, 60, and 120 min) conducted prior to randomization. Median AUC-INS was determined separately for women and men. Those above the median were considered to be relatively more IR, and those below were considered relatively more IS.

A random number generator (Microsoft Excel) was used to stratify the randomization to LF vs. LC by insulin resistance status and gender. The duration of the intervention was 6 months, and the primary outcome was 6-month weight change.

### Intervention

The intervention was a class-based education program led by a single health educator (RC). Participants were assigned to groups of 14–16 per class to follow either an LF or an LC diet. There were 14 one-hour classes over 6 months; once every week for 8 weeks, then once every other week for 8 weeks, and then once every month for 8 weeks.

**Dietary strategy.** There were four central components to the dietary strategy. The first was “how low can you go” (Limbo). LF participants were instructed to cut back to 20 g/day of total fat, and for LC to 20 g/day of digestible carbohydrate. The goal was to achieve the lowest level of fat or carbohydrate intake within the first 8 weeks. The second stage (Titrate) was to slowly add fat or carbohydrate back to the diet in increments of 5 g/day (e.g., from 20 to 25 g/day) and then hold it at that amount for 1–4 weeks before adding another 5 g/day. The third component was to identify the lowest

level of fat or carbohydrate intake participants felt could be maintained long term, potentially for the rest of their lives. The fourth strategy was to promote high nutrient density (Quality). Other Quality concepts included “real food,” “minimally processed,” “seasonal,” “organic,” “grass-fed,” “whole grain,” and “pasture-raised,” depending on diet assignment. Both diet groups received similar instructions to drink water, maximize vegetable intake, and to minimize added sugars, refined white flour products, and sources of trans fats. Participants on the LC diet were asked to consume half an avocado each day (approximately 160 kcal), as well choosing other sources of plant-based fats, including olive oil, nuts and seeds, and nut butters. Hass avocados were provided by the Hass Avocado board and were distributed to the participants. All participants were encouraged to take an active role in making food choices; by preparing their own foods at home, reading labels, and asking for appropriate modifications for restaurant menu items.

In summary, the diet strategy for both LF and LC was a “Limbo-Titrate-Quality” approach designed to motivate participants to achieve the lowest possible level of fat or carbohydrate intake i.e., equally ambitious with maximal overall nutritional quality and a dietary pattern that could be continued for a lifetime.

**Beyond fat and carbohydrate lowering.** Notably, there were no calorie restriction targets in the intervention. Participants were encouraged to track their intake using daily food journals and computer tracking programs. Although the first 8 weeks of classes focused specifically on separate strategies to lower fat or carbohydrate intake, the subsequent 4 months of classes addressed more global topics for both diet groups, similarly, such as mindful eating, adequate sleep, body acceptance, and sugar addiction.

**Physical activity.** All participants were encouraged to be physically active. Participants who were already physically active at baseline were encouraged to maintain or increase their activity. Those who were sedentary at baseline were encouraged to begin moderate exercise. All participants were given pedometers (Omron HJ-112 Digital Pocket Pedometer).

### Data collection

All data were collected at baseline and at 3 and 6 months. Clinic and laboratory staff members were blinded to treatment assignment. Participants were blinded as to their baseline OGTT results.

**Diet and physical activity data.** Three telephone-administered 24-h recall interviews were conducted at each time point using Nutrition Data System for Research (NDS-R) software [Nutrition Coordinating Center (NCC), University of Minnesota, versions 4.05.33 (2011) and 4.06.34 (2012)]. Interviews were conducted on two weekdays and one weekend day, nonconsecutive whenever possible, unannounced, during a 2-week window. Average daily energy expenditure was assessed using the Stanford 7-day physical activity recall (19).

**Anthropometric data.** Height was measured to the nearest millimeter using a standard wall-mounted stadiometer. Body weight was measured to the nearest 0.1 kg on a calibrated clinical scale. Waist circumference was measured to the nearest millimeter at the umbilicus.

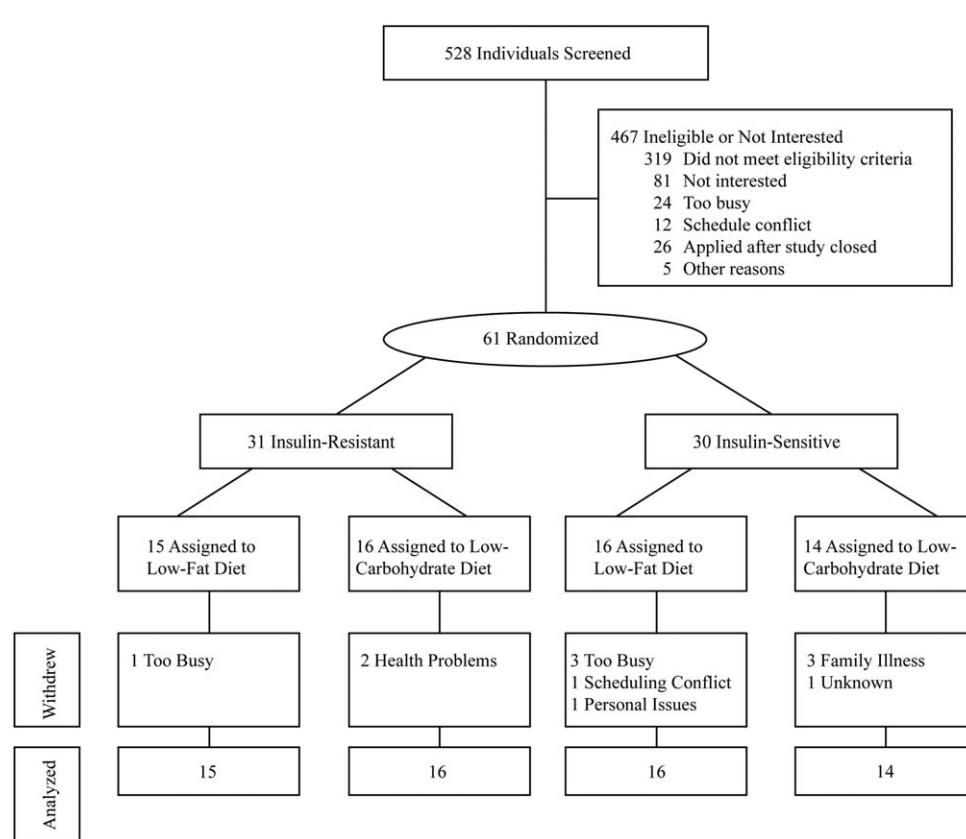


Figure 1 Participant flow through the trial.

**Metabolic measures.** Blood samples were collected after  $\geq 10$  h fast. Plasma total cholesterol and triglycerides (free glycerol blank subtracted) were measured enzymatically using established clinical chemistry laboratory methods (Northwest Lipid Laboratory, Seattle, WA) (20,21). High-density lipoprotein cholesterol (HDL-C) was measured by liquid selective detergent followed by enzymatic determination of cholesterol (22). Low-density lipoprotein cholesterol (LDL-C) was calculated according to Friedewald et al. (23). Total plasma insulin in serum was measured by radioimmunoassay (24), and blood glucose was measured using a modification of the glucose oxidase/peroxidase method (25,26) (Diabetes Research Center, Washington University, St Louis, MO). Resting blood pressure was assessed three times at 2-min intervals as described elsewhere (27); the initial reading was discarded, and the last two readings were averaged.

## Statistical methods

The primary objective was to test whether there was a significant interaction in weight loss on LF vs. LC diets by insulin resistance status as estimated by AUC-INS. Dietary composition data (energy, % carbohydrate, fat, and protein, and grams of fiber, added sugars, and saturated fat) are presented as raw, unadjusted mean ( $\pm$ SD) (i.e., no imputation for missing data).

For the main analysis, data were multiply imputed with the MICE package in R 3.0 using five imputation steps and five imputed data

sets. Each imputed data set was fit to a linear regression model using change in weight at 6 months as the outcome and with subject height, diet, insulin resistance-insulin sensitivity (IR-IS) status, and an interaction term between diet and IR-IS status as predictors. Resulting variance estimates were pooled to account for the additional variability induced by the imputation process. In a sensitivity analysis, we repeated these models after replacing the dichotomous IR-IS status with continuous baseline insulin AUC. Other exploratory analyses included the use of INS-30, INS-120, and Glu-AUC<sub>0-30</sub>  $\times$  Ins-AUC<sub>0-30</sub>. We also fit models where, instead of adjusting for baseline height, we adjusted for baseline BMI.

We also explored longitudinal differences between risk factors across the four diet  $\times$  IR-IS groups (e.g., LF-IR, LC-IR, LF-IS, and LC-IS). For each risk factor, a mixed effect model was fit with the corresponding risk factor as the outcome and group, time point and group time point interaction as predictors. Models were either linear or logistic, depending on the nature of the risk factor. For risk factors with significant interaction term *P*-values, additional pairwise comparisons among the four groups were made using Tukey's HSD test. All statistical tests were two-tailed using a significance level of 0.05.

## Results

Participants were enrolled from February to April, 2012. Sixty-one eligible participants were randomized into four groups—two classes

**TABLE 1** Baseline participant characteristics<sup>a</sup>

Variable	Insulin resistant		Insulin sensitive	
	Low-fat (n = 15)	Low-carbohydrate (n = 16)	Low-fat (n = 16)	Low-carbohydrate (n = 14)
Percent women	60	63	63	64
Age (years)	44 ± 5	42 ± 6	41 ± 6	43 ± 7
Education (years)	16.0 ± 2.0	16.4 ± 1.8	15.9 ± 3.3	16.1 ± 1.9
Percent non-white	13	13	25	0
<b>Anthropometrics</b>				
BMI (kg/m <sup>2</sup> )	35.0 ± 2.4	34.2 ± 3.8	32.6 ± 2.9	31.2 ± 1.9
Waist circumference (cm)	108.8 ± 10.4	110.0 ± 10.7	105.1 ± 9.5	98.8 ± 9.3
<b>Cardiovascular disease risk factors</b>				
LDL-C (mg/dl)	118 ± 20	108 ± 19	111 ± 30	113 ± 34
HDL-C (mg/dl)	43 ± 10	44 ± 13	51 ± 17	49 ± 14
Triglycerides (mg/dl)	146 ± 58	156 ± 68	117 ± 59	136 ± 99
Fasting insulin (μU/ml)	21 ± 5.9	27.7 ± 11.4	13.4 ± 3.1	13.4 ± 3.1
Fasting glucose (mg/dl)	100.9 ± 11.2	102.5 ± 11.8	102.7 ± 11.6	99.1 ± 7.5
Insulin AUC (μU min/ml)	130.9 ± 54	144 ± 49.5	65 ± 19	58 ± 18.4
<b>Blood pressure (mm Hg)</b>				
Systolic	122 ± 12	125 ± 10	116 ± 13	117 ± 12
Diastolic	81 ± 8	83 ± 8	77 ± 9	78 ± 7
Percent metabolic syndrome	46.67	56.25	18.75	35.71
Physical activity (kcal/kg/day)	33.2 ± 0.9	32.7 ± 1.2	34.0 ± 1.7	33.6 ± 1.4

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

<sup>a</sup>Data are expressed as mean ± SD unless otherwise indicated.

of LF and two classes of LC, with approximately 50% IR and 50% IS in each class (Figure 1). Baseline characteristics are presented in Table 1. By design, INS-AUC (and the highly correlated fasting insulin) was higher for IR vs. IS. As expected, BMI was higher among the more IR vs. IS participants, with a trend for higher triglycerides and blood pressure, lower HDL-C, and a higher percentage of metabolic syndrome in the IR group.

Average class attendance was 81% ± 13% (mean ± SD) for the LF classes and 85% ± 11% for the LC classes. Of the 61 participants enrolled, 49 (80%) completed the 6-month protocol; data were missing at 6 months from six participants in each diet group.

### Dietary adherence and physical activity

Participants in both LF and LC made substantial dietary changes as assessed at 3- and 6-months, relative to baseline (Figure 2). With average baseline energy intake percentages of 44:38:18 from carbohydrate:fat:protein, the two diet groups shifted to an average ratio of approximately 58:22 carbohydrate:fat for LF, and 21:53 for LC (average at 6 months), with protein being relatively similar, particularly at 6 months. Between the 3- and 6-month time points, there was modest recidivism in the LC group whereas macronutrient ratios were more stable for LF during this phase. Average energy intake from alcohol ranged from 1% to 4% of energy in the four LF and LC classes (energy intake from alcohol excluded from Figure 2 data). Reported energy intake suggested an average ~600 kcal/day

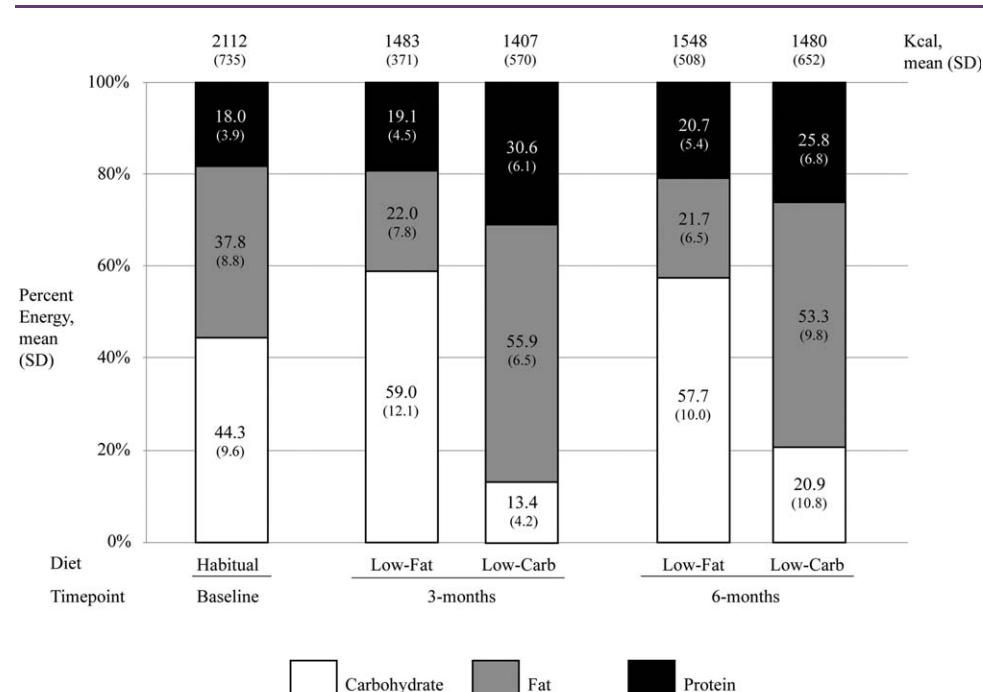
decrease at 3 and 6 months relative to baseline (~30% energy). An expanded presentation of macronutrient distribution for all four subgroups at all three time points is available in the Supporting Information Section 2 and Supporting Information Table S1.

On average, the LF group decreased absolute amounts (grams) of added sugar intake by ~50% and saturated fat by ~66% while increasing fiber intake by ~25% relative to baseline; the LC group decreased added sugar intake by ~70%, fiber by ~40%, and increased saturated fat by ~10% (Table 2). These were changes of absolute intake amounts in the context of a general ~30% reduction of overall energy intake.

Energy expenditure increased modestly and similarly for both diet groups. Baseline energy expenditure for the LF group was 33.7 ± 1.4 kcal/kg/day, which increased at 3 and 6 months to 34.2 ± 1.6 and 34.6 ± 2.6 kcal/kg/day, respectively. In parallel, baseline energy expenditure for the LC group was 32.7 ± 0.9 kcal/kg/day, which increased at 3 and 6 months to 33.5 ± 1.3 and 33.8 ± 1.9 kcal/kg/day, respectively.

### Six-month weight loss for four groups

Average weight loss after 6 months for the n = 49 that completed the protocol was 9.0 ± 6.5 kg (19.8 ± 14.3 lbs), which represented 8.9 ± 5.7% of baseline weight. The 6-month weight loss results by diet type and IR-IS status group were 7.5 ± 6.0 kg for LF-IR,



**Figure 2** Dietary assessment: proportions of carbohydrates, fats, and proteins for each diet at baseline, 3 months, and 6 months.

$10.4 \pm 7.8$  kg for LF-IS,  $9.6 \pm 6.6$  kg for LC-IR, and  $8.6 \pm 5.6$  kg for LC-IS (Figure 3). A significant interaction between diet assignment and IR-IS status was not detected, and there were no significant main effect differences in weight loss detected by diet group or by IR-IS status. We found no meaningful differences in estimate direction or significance between the models where baseline height was a confounder and models where baseline BMI was a confounder or when using INS-30, INS-120, or Glu-AUC<sub>0-30</sub> × Ins-AUC<sub>0-30</sub> in the models.

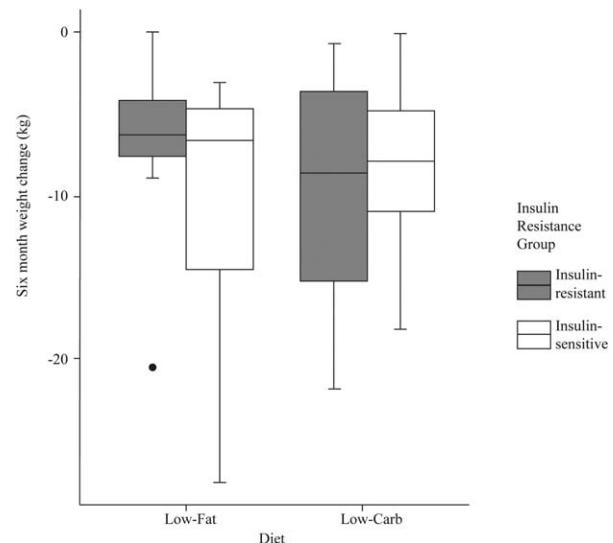
**TABLE 2** Selected dietary components (mean  $\pm$  SD)<sup>a</sup>

	Low-fat	Low-carbohydrate
Total fiber (g/1000 kcal)		
Baseline	$9 \pm 4$	$12 \pm 5$
3 months	$18 \pm 8$	$9 \pm 3$
6 months	$16 \pm 7$	$10 \pm 4$
Added sugars (g/1000 kcal)		
Baseline	$20 \pm 10$	$19 \pm 10$
3 months	$16 \pm 11$	$4 \pm 4$
6 months	$16 \pm 13$	$7 \pm 6$
Saturated fat (g/1000 kcal)		
Baseline	$15 \pm 4$	$13 \pm 4$
3 months	$7 \pm 3$	$20 \pm 5$
6 months	$7 \pm 3$	$19 \pm 6$

<sup>a</sup>Sample sizes: baseline low-fat  $n = 31$  and low-carbohydrate  $n = 30$ ; 3 months  $n = 26$  for each diet group; 6 months  $n = 25$  for each group.

### Risk factor changes

With few exceptions, risk factors changed in a beneficial way across all groups (Table 3). Triglyceride concentrations dropped by  $\sim 25\%$  across the four groups combined. Both diastolic and systolic blood pressure decreased for all four groups. HDL-C concentrations



**Figure 3** Six-month weight change by diet and insulin resistance group,  $n = 49$ . Six-month weight loss (kg) was  $7.4 \pm 6.0$  (LF-IR),  $10.4 \pm 7.8$  (LF-IS),  $9.6 \pm 6.6$  (LC-IR), and  $8.6 \pm 5.6$  (LC-IS).

**TABLE 3** Risk factor changes and metabolic syndrome prevalence by diet group-insulin resistance status

	Insulin resistant		Insulin sensitive		P-value (time × treatment group) <sup>†</sup>
	Low-fat (n = 15*)	Low-carbohydrate (n = 16*)	Low-fat (n = 16*)	Low-carbohydrate (n = 14*)	
<b>Risk factor changes</b>					
LDL-C (mg/dl)					
3 months	−13.2 (20.1)	12.6 (21.0)	−16.2 (27.8)	23.9 (46.6)	
6 months	−14.4 (23.8) <sup>a,b</sup>	6.5 (25.7) <sup>a,b</sup>	−20.8 (26.1) <sup>a</sup>	17.8 (40.8) <sup>b</sup>	0.006
HDL-C (mg/dl)					
3 months	−2.6 (6.0)	0.1 (4.8)	−3.5 (6.5)	2.1 (6.6)	
6 months	3.7 (5.9)	4.3 (3.7)	0.6 (5.8)	4.4 (7.0)	0.273
Triglycerides (mg/dl)					
3 months	−8.1 (39.5)	−40.1 (77.9)	−12.8 (23.0)	−20.9 (33.9)	
6 months	−34.1 (30.1)	−35.1 (67.4)	−9.6 (27.9)	−32.2 (41.4)	0.588
Fasting insulin (μU/mL)					
6 months	−8.2 (5.6) <sup>a,b</sup>	−12.7 (8.1) <sup>a</sup>	−4.5 (4.4) <sup>b</sup>	−3.8 (3.8) <sup>b</sup>	0.003
Fasting glucose (mg/dl)					
3 months	−5.0 (10.3)	−4.6 (12.9)	−8.1 (10.7)	0.8 (8.7)	
6 months	−2.8 (10.0)	−5.7 (13.6)	−3.6 (16.5)	3.8 (7.8)	0.125
Insulin AUC (μU min/ml)					
3 months	−65.8 (4.9)	−68.3 (50.1)	−27.5 (25.4)	−11.2 (23.6)	
6 months	−57.6 (38.4) <sup>a,c</sup>	−67.5 (49.3) <sup>a</sup>	−15.1 (32.7) <sup>b</sup>	−18.3 (20.5) <sup>b,c</sup>	<0.0001
Blood pressure systolic (mm Hg)					
3 months	−1.1 (5.2)	−6.7 (11.9)	−3.8 (6.3)	−6.0 (7.4)	
6 months	−2.2 (9.0)	−8.8 (10.1)	−6.9 (10.2)	−4.4 (8.1)	0.165
Blood pressure diastolic (mm Hg)					
3 months	−0.7 (3.8)	−3.8 (7.3)	−3.7 (4.3)	−3.8 (4.3)	
6 months	−2.4 (6.8)	−5.3 (7.5)	−6.4 (7.1)	−4.3 (5.6)	0.311
<b>Prevalence</b>					
Metabolic syndrome (%)					
3 months	46.7	18.8	6.3	14.3	
6 months	20.0	12.5	12.5	7.1	0.508

Data are expressed as mean (SD), except for metabolic syndrome (%).

\*Table column headings indicate sample size used in statistical testing. Values reflect actual data from those who completed the 6-month protocol: n = 14, n = 14, n = 11, and n = 10, respectively.

<sup>†</sup>Intention-to-treat analysis, with baseline data carried forward for missing values. P-value for time × diet group interaction for 6-month change determined using mixed-model and autoregressive covariance structure.

<sup>a,b,c</sup>For 6-month risk factors with time × group P < 0.05, pair-wise differences are indicated by superscripts; pairs with a shared superscript are not different.

increased by almost 10% in three of the four groups, with a negligible overall change in the LF-IS group. Fasting glucose decreased modestly, on average, in three of the four groups, with a negligible 6-month change in the LC-IS group. At baseline 40% of participants met metabolic syndrome criteria, which was down to 15% overall at 6 months. No significant 6-month change differences were detected among groups for any of the above risk factors.

Six-month changes in LDL-C concentrations were statistically different among groups, with decreases for LF and increases for LC, regardless of IR-IS status. Fasting insulin concentrations dropped significantly more for the two IR groups than the two IS groups, although by definition the IR groups had higher baseline insulin levels and thus greater capacity for improvement. Overall average fasting insulin concentrations decreased for all four groups. This same pattern was observed for INS-AUC.

## Discussion

In this pilot study, we investigated whether there was a differential weight loss response to LF vs. LC diets by baseline IR-IS status, using INS-AUC as a proxy measure, among nondiabetic overweight adults and adults with obesity who were otherwise in general good health. Overall, participants experienced substantial weight loss: an average of  $9.0 \pm 6.5$  kg, which represented  $8.9 \pm 5.7\%$  of baseline weight. However, a significant interaction between diet assignment and IR-IS status was not detected for weight loss. Dietary assessment indicated substantial diet differentiation between the LF and LC groups, which was supported by observed changes in secondary metabolic outcomes, including fasting insulin, LDL-C, HDL-C, and triglycerides. In addition, the dietary assessment data indicate that the substantial dietary changes achieved by mid-study were largely maintained to the end of the study at 6 months.

Several other studies have reported a statistically significant interaction in weight loss between diet type and IR-IS status, including a previous investigation by our own research group (8-10,12). Two of the studies were feeding studies, of 4-6 month duration with small sample sizes of four to eight per treatment arm (8,12). These studies, perhaps because of the more rigorous control of diet, and the 30% restriction of energy intake, achieved greater weight loss overall than the two free-living studies which used an *ad libitum* approach (9,10). However, the free-living studies had larger sample sizes and longer durations than the feeding studies. Notably, the four previous studies used three different methods to assess insulin and glucose dynamics. Compared with this set of four previous studies, in this free-living study, the magnitude of overall weight loss was comparable to the feeding studies and substantially higher than the other two free-living studies while using an *ad libitum* approach to energy intake. The INS-AUC method used in this study to differentiate greater IR from greater IS individuals was different than all of the other studies, and was more a measure of hyperinsulinemia than a direct measure of insulin resistance. In absolute numbers, the average weight loss results in this study paralleled the findings from the other studies—the more IR group lost slightly more weight on LC, and the IS group lost slightly more weight on LF, but the differences were not statistically or clinically significant. With so many differences among the previous four studies and this study, which all address the same general research question, we are not able to determine whether we failed to detect a true effect that the other studies correctly identified, or if we truly and accurately identified no effect in our study population using the design described.

There are multiple mechanisms that could be responsible for a potential differential weight loss response to LF vs. LC diets by variability in insulin and glucose dynamics, including differential hunger/satiety, energy expenditure, fatty-acid metabolism, lipolysis, and adipogenesis. Several groups of investigators have observed one or more factors along a continuum that suggest LF relative to LC diets cause greater excursions in postprandial glucose and insulin metabolism, may increase 24-h hunger, and may subsequently increase overall energy intake due to their higher glycemic load (11,28-31). Related research suggests that diets with a higher glycemic index can affect hormones regulating metabolism (13-15). Under these conditions, IR individuals may feel less satisfied and experience stronger physiologically driven urges to consume more food after consuming a lower fat/higher carbohydrate meal compared with IS individuals.

In separate experiments with humans, one a parallel design and another a cross-over, the lab group of Ludwig and coworkers found that substantial weight loss achieved by or followed by isocaloric diets differing in glycemic load led to differential changes in resting energy expenditure and total energy expenditure; the observed results favored greater energy expenditure on the lower glycemic load/lower carbohydrate diets (17,32). Although IR-IS status was not addressed as a potential covariate in these analyses, it is plausible that the more IR individuals who were on higher glycemic load/higher carbohydrate diets would experience an even greater decrease in energy expenditure than the more IS individuals on the same diet, making it more difficult to achieve or maintain weight loss.

Further discussion of the observed changes and lack of changes in some of the risk factors in Table 3 is presented in the Supporting Information Section 3.

The study design and conduct included several important strengths. One was the high degree of dietary differentiation achieved for those assigned to LF vs. LC. In many weight loss diet studies, the combination of modest dietary goals and substantial recidivism over time (i.e., weak treatment fidelity) can lead to a lack of physiologically meaningful dietary differences between treatment arms. The differences in proportions of energy intake from fat vs. carbohydrate achieved and maintained out to 6 months in the two diet groups of this study involved a substantial shift of approximately 25% of energy intake. The use of three unannounced 24-h recalls and NDS-R for dietary assessment at three time points, and the high rate of completion of these assessments was an important methodological strength. Other strengths included the relatively high retention rate of 80% and the identical drop-out rates in both diets. Stratifying the randomization by IR-IS status was an important design component, and the use of INS-AUC from OGTTs to identify and differentiate participants who were more IR vs. more IS was superior to fasting measures that could have been used (e.g., fasting insulin or TG/HDL-C ratio).

The major limitations of this pilot study were the duration and sample size. Given a consistent pattern of maximal weight loss at 6 months followed by weight stabilization and often regain across a range of published studies, it is more optimal to include follow-ups of a year or more in weight loss studies. Also, given the substantial heterogeneity of intergroup weight loss typical of these types of trials, large sample sizes are a preferred design component; the null finding for an interaction between IR-IS status and diet assignment for weight loss difference in this study may have been attributable to a lack of adequate statistical power. However, a primary objective of this pilot study was to test the approach undertaken to achieve greater differentiation of diets and treatment fidelity for the purpose of incorporating this approach in a future, larger, longer trial; that follow-up trial, with a sample size of 600 and duration of 1 year is currently underway. An expanded discussion of study limitations is presented in the Supporting Information Section 4. Despite the limitations of the pilot study, we believe the high degree of apparent treatment diet differentiation, the relatively high average weight loss across both treatment arms, and the interesting findings of risk factor changes at 3 and 6 months are results worthy of dissemination.

In conclusion, our pilot study achieved substantial differentiation of LF vs. LC study diets in a free-living population that led to an average weight loss of 9% body weight over 6 months in overweight adults and adults with obesity. Our findings did not detect differential effects by diet, by IR-IS status, or the interaction of these conditions. Further research on a larger study population for a longer period of time is warranted using the novel dietary intervention approach developed here. O

## Acknowledgments

The authors acknowledge Antonella Dewell, Josephine Hau, and Taylor Saunders for coordinating the implementation of the study and for data collection, Jessica Kubo for her contribution to statistical analysis and data management, Alana Koehler for her technical support, and all of the research participants without whom the study would not have been possible.

© 2015 The Obesity Society

## References

1. Centers for Disease Control and Prevention. Overweight and obesity [Webpage]. 2014 [updated September 9, 2014]. Available at: <http://www.cdc.gov/obesity/data/adult.html>.
2. McLaughlin T, Abbasi F, Lamendola C, Reaven G. Heterogeneity in the prevalence of risk factors for cardiovascular disease and type 2 diabetes mellitus in obese individuals: effect of differences in insulin sensitivity. *Arch Intern Med* 2007;167:642-648.
3. Reaven GM. The insulin resistance syndrome: definition and dietary approaches to treatment. *Annu Rev Nutr* 2005;25:391-406.
4. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. National Institutes of Health. *Obes Res* 1998;6(Suppl 2): 51S-209S.
5. Agatston A. *The South Beach Diet*. New York: St. Martin's Griffin; 2005.
6. Atkins RC. *Dr. Atkins' New Diet Revolution*. New York: Harper Collins; 2009.
7. Sears B. *The Zone: A Dietary Road Map*. New York: Regan Books; 1995.
8. Cornier MA, Donahoo WT, Pereira R, et al. Insulin sensitivity determines the effectiveness of dietary macronutrient composition on weight loss in obese women. *Obes Res* 2005;13:703-709.
9. Ebbeling CB, Leidig MM, Feldman HA, Lovesky MM, Ludwig DS. Effects of a low-glycemic load vs. low-fat diet in obese young adults: a randomized trial. *JAMA* 2007;297:2092-2102.
10. McClain AD, Otten JJ, Hekler EB, Gardner CD. Adherence to a low-fat vs. low-carbohydrate diet differs by insulin resistance status. *Diabetes Obes Metab* 2013;15:87-90.
11. McLaughlin T, Carter S, Lamendola C, et al. Effects of moderate variations in macronutrient composition on weight loss and reduction in cardiovascular disease risk in obese, insulin-resistant adults. *Am J Clin Nutr* 2006;84:813-821.
12. Pittas AG, Das SK, Hajduk CL, et al. A low-glycemic load diet facilitates greater weight loss in overweight adults with high insulin secretion but not in overweight adults with low insulin secretion in the CALERIE trial. *Diabetes Care* 2005;28:2939-2941.
13. Boden G, Sargrad K, Homko C, Mozzoli M, Stein TP. Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. *Ann Intern Med* 2005;142:403-411.
14. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA* 2002;287:2414-2423.
15. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. *Pediatrics* 1999;103:E26.
16. Pawlak DB, Kushner JA, Ludwig DS. Effects of dietary glycaemic index on adiposity, glucose homeostasis, and plasma lipids in animals. *Lancet* 2004;364:778-785.
17. Pereira MA, Swain J, Goldfine AB, Rifai N, Ludwig DS. Effects of a low-glycemic load diet on resting energy expenditure and heart disease risk factors during weight loss. *JAMA* 2004;292:2482-2490.
18. Rodin J. Insulin levels, hunger, and food intake: an example of feedback loops in body weight regulation. *Health Psychol* 1985;4:1-24.
19. Sallis JF, Haskell WL, Wood PD, et al. Physical activity assessment methodology in the Five-City Project. *Am J Epidemiol* 1985;121:91-106.
20. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. *Clin Chem* 1974;20:470-475.
21. Sampson EJ, Demers LM, Krieg AF. Faster enzymatic procedure for serum triglycerides. *Clin Chem* 1975;21:1983-1985.
22. Warnick GR, Albers JJ. A comprehensive evaluation of the heparin-manganese precipitation procedure for estimating high density lipoprotein cholesterol. *J Lipid Res* 1978;19:65-76.
23. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499-502.
24. Morgan CR, Lazarow A. Immunoassay of insulin: two antibody system: plasma insulin levels in normal, sub diabetic, and diabetic rats. *Diabetes* 1963;12:115-126.
25. Lott JA, Turner K. Evaluation of Trinder's glucose oxidase method for measuring glucose in serum and urine. *Clin Chem* 1975;21:1754-1760.
26. Trinder P. Determination of blood glucose using an oxidase-peroxidase system with a non-carcinogenic chromogen. *J Clin Pathol* 1969;22:158-161.
27. King AC, Sallis JF, Dunn AL, et al. Overview of the Activity Counseling Trial (ACT) intervention for promoting physical activity in primary health care settings. Activity Counseling Trial Research Group. *Med Sci Sports Exerc* 1998;30:1086-1096.
28. Arumugam V, Lee JS, Nowak JK, et al. A high-glycemic meal pattern elicited increased subjective appetite sensations in overweight and obese women. *Appetite* 2008;50:215-222.
29. Lennerz BS, Alsop DC, Holsen LM, et al. Effects of dietary glycemic index on brain regions related to reward and craving in men. *Am J Clin Nutr* 2013;98:641-647.
30. Liu AG, Most MM, Brashears MM, Johnson WD, Cefalu WT, Greenway FL. Reducing the glycemic index or carbohydrate content of mixed meals reduces postprandial glycemia and insulinemia over the entire day but does not affect satiety. *Diabetes Care* 2012;35:1633-1637.
31. Shikany JM, Margolis KL, Pettiner M, et al. Effects of a low-fat dietary intervention on glucose, insulin, and insulin resistance in the Women's Health Initiative (WHI) Dietary Modification trial. *Am J Clin Nutr* 2011;94:75-85.
32. Ebbeling CB, Swain JF, Feldman HA, et al. Effects of dietary composition on energy expenditure during weight-loss maintenance. *JAMA* 2012;307:2627-2634.

# Long-term effects of weight loss with a very low carbohydrate and low fat diet on vascular function in overweight and obese patients

■ T. P. Wycherley<sup>1,2</sup>, G. D. Brinkworth<sup>1</sup>, J. B. Keogh<sup>1</sup>, M. Noakes<sup>1</sup>, J. D. Buckley<sup>3</sup> & P. M. Clifton<sup>1</sup>

From the <sup>1</sup>Preventative Health Flagship, Commonwealth Scientific and Industrial Research Organisation, Food and Nutritional Sciences, Adelaide, SA, Australia, <sup>2</sup>Department of Physiology, School of Molecular and Biomedical Science, University of Adelaide, Adelaide, SA, Australia, <sup>3</sup>Nutritional Physiology Research Centre and Australian Technology Network Centre for Metabolic Fitness, Sansom Institute for Health Research, University of South Australia, Adelaide, SA, Australia

**Abstract.** Wycherley TP, Brinkworth GD, Keogh JB, Noakes M, Buckley JD, Clifton PM. (Commonwealth Scientific and Industrial Research Organization, Food and Nutritional Sciences; School of Molecular and Biomedical Science, University of Adelaide; and Nutritional Physiology Research Centre and Australian Technology Network Centre for Metabolic Fitness, Sansom Institute for Health Research, University of South Australia). Long-term effects of weight loss with a very low carbohydrate and low fat diet on vascular function in overweight and obese patients. *J Intern Med* 2010; **267**: 452–461.

**Objective.** To compare the effects of an energy reduced very low carbohydrate, high saturated fat diet (LC) and an isocaloric high carbohydrate, low fat diet (LF) on endothelial function after 12 months.

**Design and Subjects.** Forty-nine overweight or obese patients (age  $50.0 \pm 1.1$  years, BMI  $33.7 \pm 0.6$  kg m $^{-2}$ ) were randomized to either an energy restricted ( $\sim 6\text{--}7$  MJ), planned isocaloric LC or LF for 52 weeks. Body weight, endothelium-derived factors, flow-mediated dilatation (FMD), adiponectin, augmentation index (AIx) and pulse wave

velocity (PWV) were assessed. All data are mean  $\pm$  SEM.

**Results.** Weight loss was similar in both groups (LC  $-14.9 \pm 2.1$  kg, LF  $-11.5 \pm 1.5$  kg;  $P = 0.20$ ). There was a significant time  $\times$  diet effect for FMD ( $P = 0.045$ ); FMD decreased in LC ( $5.7 \pm 0.7\%$  to  $3.7 \pm 0.5\%$ ) but remained unchanged in LF ( $5.9 \pm 0.5\%$  to  $5.5 \pm 0.7\%$ ). PWV improved in both groups (LC  $-1.4 \pm 0.6$  m s $^{-1}$ , LF  $-1.5 \pm 0.6$  m s $^{-1}$ ;  $P = 0.001$  for time) with no diet effect ( $P = 0.80$ ). AIx and VCAM-1 did not change in either group. Adiponectin, eSelectin, tPA and PAI-1 improved similarly in both groups ( $P < 0.01$  for time).

**Conclusion.** Both LC and LF hypoenergetic diets achieved similar reductions in body weight and were associated with improvements in PWV and a number of endothelium-derived factors. However, the LC diet impaired FMD suggesting chronic consumption of a LC diet may have detrimental effects on endothelial function.

**Keywords:** cardiovascular disease, endothelial function, flow-mediated dilatation.

## Introduction

Although current weight loss recommendations are to consume a moderate hypocaloric, high carbohydrate, low fat diet (LF) [1], the obesity epidemic has led to a rise in the use of alternate dietary patterns, particularly very low carbohydrate diets (LC) [2]. As LC diets, such as the 'Atkins diet' are typically high in saturated fat, concern remains about their potential effects on cardiovascular disease risk [3]. Several long-term studies demonstrate that although weight loss following a LC or LF diet produce similar

improvements in blood pressure and fasting glucose and insulin, differential effects occurs on blood lipids [4–8]. Compared with a LF diet, LC diets favourably decrease triglycerides and increase high-density lipoprotein cholesterol (HDL-C) levels, but in some studies [9] also produce increases in total cholesterol and low-density lipoprotein cholesterol (LDL-C). Hence, some debate still exists regarding the effects of these diets on overall cardiovascular disease (CVD) risk. Traditional cardiometabolic markers account for only a proportion of total CVD risk [10] and there is a greater need to assess the impact of dietary

composition on other CVD risk markers to help characterize the effects of LC diets on CVD risk.

Recently, a number of endothelial biochemical markers have been identified and implicated in the pathogenesis of atherosclerosis and CVD [11–14]. Cellular adhesion molecules including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and eSelectin are generally accepted to be associated with the pathogenesis of atherosclerosis and are predictors of clinical events [11]. These endothelial markers are elevated in obesity and have been shown to be consistently reduced with weight loss via caloric restriction [15, 16]. Similarly, endothelium-derived fibrinolytic factors including plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA) are associated with atherosclerosis [12, 13] and have shown to be elevated in obesity and improved with weight loss [17]. Adiponectin, an adipokine that modulates lipid and glucose metabolism [18], is unfavourably decreased in obesity [14] and can improve with long-term weight loss [8, 15]. The changes associated in these vascular markers with weight loss appear to occur independently of diet composition [15, 16, 19], although to date no study has examined the long-term effects of LC diets on these markers.

Brachial artery flow-mediated dilatation (FMD) is a functional marker of endothelial function, which is impaired in obesity [20] and is emerging as an important prognostic factor for future cardiac events [21]. Acute meal studies have shown that a high saturated fat meal can impair FMD [22, 23]. A previous study showed 3 weeks consumption of a high saturated fat diet in energy balance impaired FMD [24]. Similarly, Miller *et al.* [25] showed an LC ‘Atkins’, energy balance diet impaired FMD after 4 weeks which was negatively associated with saturated fat intake. Conversely, two further studies have shown a Mediterranean, high monounsaturated fat diet improved FMD [26, 27]. To date, only three studies have assessed the effects of a LC diet on FMD during weight loss and have reported equivocal results [19, 28, 29]. Two separate studies reported no change in FMD after 8-weeks of either an energy-restricted LC or an isocaloric LF diet [19, 29]. In contrast, Phillips *et al.* [28] showed that after 6-weeks, FMD improved with an energy-restricted LF diet but was impaired with a LC ‘Atkins’ diet. To date no known study has evaluated the long-term effects of an energy-restricted LC diet on FMD. Such information would make a significant contribution to the understanding of the chronic effects of these dietary patterns

that has been in urgent demand and clinicians need to be aware of.

The aim of this study was to compare the effects of an energy restricted, high saturated fat LC diet and an isocaloric conventional LF diet on FMD and markers of vascular function after 12 months.

## Methods

### Participants

The participants and study design have been previously described in a study reporting separate outcomes [7]. The study was approved by the human ethics committees of the Commonwealth Scientific and Industrial Research Organization (CSIRO) and the University of South Australia and all participants provided written informed consent prior to study commencement. Briefly, 118 volunteers (122 recruited, four withdrew prior to randomization) aged 24–64 years and BMI between 26 and 43 kg m<sup>-2</sup>, with abdominal obesity and at least one additional metabolic syndrome risk factor [30], were randomized to consume either an energy-restricted LC diet ( $n = 57$ ) or an isocaloric conventional LF diet ( $n = 61$ ) for 52-weeks. Exclusion criteria were a history of liver, cardiovascular, peripheral vascular, respiratory, or gastrointestinal disease; diabetes, pregnancy; a malignancy or smoking. Eleven participants (LC = 2 and LF = 9) withdrew prior to study commencement and a further 38 (LC = 16, LF = 22) dropped out by 1-year. Of the remaining 69 participants, 49 (LC = 26; LF = 23) completed the vascular function assessments and are reported in the current investigation (Table 1).

Participants on the LC diet were prescribed a dietary plan that provided 4% of total energy from carbohydrate (CHO), 35% as protein and 61% as fat (20% saturated fat) with the objective to restrict carbohydrate to <20 g day<sup>-1</sup> for the first 8-weeks with an option to increase to <40 g day<sup>-1</sup> for the remainder of the study. For participants on the LF diet the prescribed dietary profile was 46% of total energy as carbohydrate, 24% as protein, 30% as total fat (<8% saturated fat) with the objective to restrict saturated fat intake to <10 g day<sup>-1</sup> for the study duration, with the inclusion of an approved food exchange (equivalent to the energy content of 20 g of carbohydrate) between weeks 8 and 52. Both diets were designed to be isocaloric with moderate energy restriction (~6000 kJ day<sup>-1</sup> for women and ~7000 kJ day<sup>-1</sup> for men). To maximize retention and monitor

**Table 1** Baseline participant characteristics

Variable	LC	LF
<i>N</i>	26	23
Age (years)	49.9 ± 1.7	50.2 ± 1.4
Gender (no. male/female)	8/18	9/14
Weight (kg)	94.2 ± 3.2	97.5 ± 2.7
Body mass index (kg m <sup>-2</sup> )	33.5 ± 0.8	33.9 ± 0.8
Waist circumference (cm)		
Male	111.8 ± 3.9	110.8 ± 1.8
Female	100.6 ± 2.0	102.0 ± 2.9
Blood pressure (mmHg)		
Systolic	134 ± 3	137 ± 3
Diastolic	73 ± 3	78 ± 3
Elevated blood pressure [n (%)]	17 (65)	18 (78)
Antihypertensive Medication [n (%)]	9 (35)	7 (30)
Elevate fasting blood glucose [n (%)]	9 (35)	7 (30)
Elevated triglycerides [n (%)]	14 (54)	12 (52)
Reduced HDL-C [n (%)]	4 (15)	3 (13)
Lipid lowering medication [n (%)]	6 (23)	4 (17)
Metabolic syndrome [n (%)]	14 (54)	11 (48)

LC, very low carbohydrate diet group; LF, low fat diet group; HDL-C, high-density lipoprotein cholesterol. Metabolic risk factors and the metabolic syndrome were defined according to the criteria of the International Diabetes Federation.[30] No participants were taking hypoglycaemic medications. The characteristics of the participants were not significantly different between diet groups by chi-square and independent *t*-tests. All values are mean ± SEM.

compliance participants attended the clinic for consultations with a qualified dietitian, fortnightly for the first 8-weeks and monthly thereafter, to review their progress and receive dietary advice. Both dietary patterns were structured to include specific food quantities to ensure the correct macronutrient and energy requirements were achieved [19]. Foods were listed in a semi-quantitative food record which participants completed daily. Dietary composition was assessed using 3 days of randomly selected daily food records per fortnight (2 weekdays and 1 weekend day) and analysed using computerized dietary software (Foodworks Professional Edition, version 4 software, Xyris Software 1998, Highgate Hill, Australia). Food intake variables were expressed as an average of the analysed food records from Week 0 to Week 52.

#### Data collection and physiological assessments

At baseline (Week 0) and Week 52, participants attended the CSIRO clinical research unit after an overnight fast for clinical assessments. Participants were asked to abstain from alcohol consumption and participation in vigorous physical activity during the 24-h prior to these visits. Body weight was measured using calibrated electronic digital scales (Mercury, AMZ 14, Tokyo, Japan) and seated blood pressure was assessed using an automated sphygmomanometer (DYNAMAP™ 8100; Criticon, Tampa, FL, USA).

Endothelium-dependent brachial artery FMD was measured under conditions previously described [31]. B-mode ultrasound with a 7.5 MHz linear array transducer (Accuson Aspen Duplex, Mountain View, CA, USA) was used to image the brachial artery in the distal third of the arm. A sphygmomanometer cuff was placed around the forearm 2 cm distal to the olecranon process and inflated to 200 mmHg for 5 min to provide forearm ischaemia. Images were video recorded 30 s before cuff deflation and every 15 s for 3 min after deflation. The flow-mediated dilatory response expressed as a percentage change of the baseline diameter of the artery was used as the measure of endothelium-dependent vasodilation. After a 10 min rest endothelium-independent dilatation was assessed after the administration of 300 µg sublingual glyceryl-trinitrate. Images were video recorded 30 s before administration of glyceryl-trinitrate and every minute for 10-min following. All FMD assessments were performed and analysed by the same operator, and the intra-observer coefficient of variation for FMD in this operator's hands was 10.6% based on data for normal healthy individuals (*n* = 10) who were scanned on two separate occasions after an overnight fast prior to commencement of the study, which is similar to that reported in other laboratories [32, 33].

AIx was assessed using the SphygmoCor™ blood pressure analysis system (AtCor Medical, Sydney, Australia), which assesses the aortic pulse waveform, AIx, and derives central aortic pressures using applanation tonometry of the radial artery. The radial pressure waveform was recorded with a micro manometer (Millar SPT-301; Millar instruments, Houston, TX, USA) and calibrated with a peripheral blood pressure value of the brachial artery (DYNAMAP™ 8100; Criticon). Ascending aortic pressure was derived from the central pressure waveform, using a generalized transfer function that is incorporated in the SphygmoCor™ device. AIx was calculated as the

difference between early and late pressure peaks divided by pulse pressure, and expressed as a percentage ( $CV = 16.5\%$ ).

Pulse wave velocity was measured via Doppler recordings at the carotid and femoral arteries (Accuson Aspen Duplex). A simultaneous electrocardiogram recording was used to calculate the interval between the R-wave and the upstroke of the associated sound wave. Approximately 10 consecutive heart beats were recorded to cover a complete respiratory cycle. Pulse wave velocity was calculated as the difference between the average intervals of each artery, divided by the measured surface distance ( $CV = 11.3\%$ ).

Research personnel who performed the outcomes assessments (data collectors and data analysts) were blinded to treatment assignment to minimize operator bias.

#### *Biochemical analysis*

A fasting blood sample was collected for measurement of serum lipids (total cholesterol, HDL-C, LDL-C, triglycerides), plasma B12, plasma folate, plasma homocysteine, serum adiponectin and serum markers of vascular function (PAI-1, tPA, ICAM-1, VCAM-1, eSelectin). Biochemical assays were performed in a single assay at the completion of the study. Serum lipids were measured using enzymatic kits (Roche Diagnostics, Indianapolis, IN, USA) on an automated analyser (Boehringer Mannheim/Hitachi 902; Hitachi Science Systems, Ltd. Ibaraki, Japan) (within assay CV's: Total Cholesterol = 0.8%, HDL = 0.9%, Triglycerides = 1.5%). The Friedewald equation was used to calculate LDL-C concentrations [34]. Serum eSelectin, VCAM-1, ICAM-1, PAI-1 and adiponectin were measured using a commercial multiplex kit (Lincoplex human CVD 5 plex; Linco Research, MS, USA) (within assay CV's: eSelectin = 11.2%, VCAM-1 = 4.5%, ICAM-1 = 7.9%, PAI-1 = 11.8%, Adiponectin = 9.2%). Serum tPA was measured in duplicate using a commercial enzyme-linked immunoassay kit (BMS258/2; Bender Medsystems, Vienna, Austria) (within assay CV = 3.6%). Plasma B12, folate and homocysteine were measured in a certified commercial laboratory (Institute of Medical and Veterinary Sciences, Adelaide, South Australia, Australia.).

#### *Statistical analysis*

Statistical analyses were performed using SPSS for Windows (Version 16.0, SPSS, Chicago, IL). Prior to

hypothesis testing, data were examined for normality. Distribution was normal except for PWV, AIx and triglycerides which were normalized using logarithmic transformation before analysis with normal-scale values presented. Unpaired *t*-tests were used to assess differences at baseline for continuous variables and chi-square tests for categorical variables. The effects of the dietary intervention was assessed by using repeated measures analysis of variance (anova) with time as the within-participant factor and diet and gender as the between participant factors. No effect of gender was observed for any of the outcome variables assessed. Pearson's correlation coefficients were used to determine the relations of the changes between variables. Statistical significance was set at  $P < 0.05$ , data are presented as mean  $\pm$  SEM.

#### **Results**

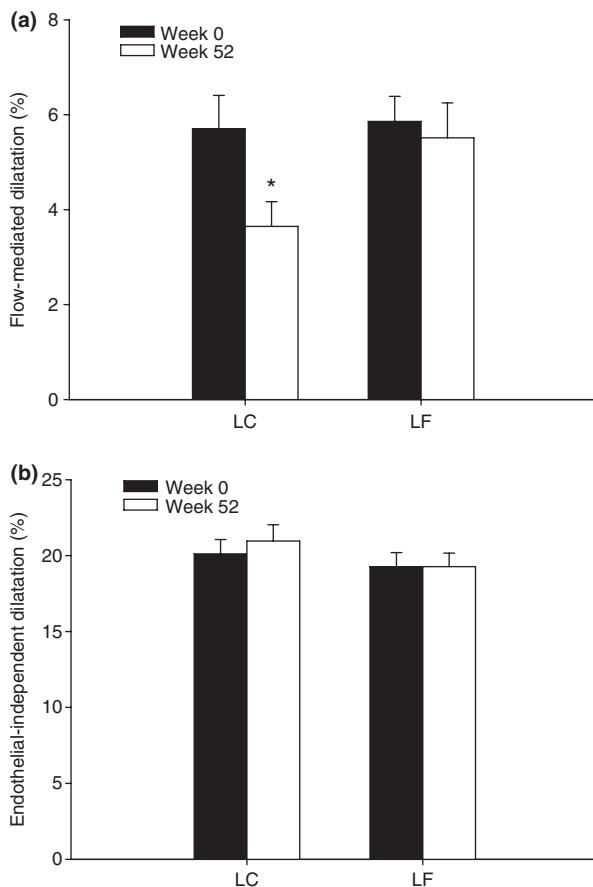
##### *Dietary compliance and medication changes*

Dietary records indicated dietary compliance was consistent with the prescribed dietary patterns. Energy intake was similar in both dietary groups (LC  $6694 \pm 126$  kJ day $^{-1}$ , LF  $6433 \pm 189$  kJ day $^{-1}$ ;  $P = 0.25$ ) however, in the LC diet CHO intake was significantly lower (LC  $30.4 \pm 2.2$  g day $^{-1}$ , LF  $166.9 \pm 8.7$  g day $^{-1}$ ;  $P < 0.001$ ) and intake of protein (LC  $130.4 \pm 2.2$  g day $^{-1}$ , LF  $87.7 \pm 3.4$  g day $^{-1}$ ;  $P < 0.001$ ) total fat (LC  $102.1 \pm 2.7$  g day $^{-1}$ , LF  $47.4 \pm 4.3$  g day $^{-1}$ ;  $P < 0.001$ ) and saturated fat (LC  $37.3 \pm 1.1$  g day $^{-1}$ , LF  $11.4 \pm 1.5$  g day $^{-1}$ ;  $P < 0.001$ ) were significantly higher.

During the intervention five participants had increased (LC = 3, LF = 2) and seven participants had decreased (LC = 4, LF = 3) their antihypertensive medication. One participant in the LC diet group increased and one participant in the LC diet group decreased their lipid lowering medication. There was no difference between the diet groups for changes in medication ( $P > 0.34$ ).

##### *Flow-mediated dilatation, pulse wave velocity and augmentation index*

At Week 0, there was no difference between groups in brachial artery FMD (LC:  $5.7 \pm 0.7\%$  LF:  $5.9 \pm 0.5\%$ ;  $P = 0.86$ ). Following the intervention, there was a significant treatment  $\times$  time effect ( $P = 0.045$ ), such that FMD decreased in the LC diet ( $-2.1 \pm 0.6\%$ ) but remained unchanged in the LF diet group ( $-0.3 \pm 0.6\%$ , Fig. 1). The endothelium-independent vasodilatory response to glyceryl-trinitrate was not



**Fig. 1** Brachial artery flow-mediated dilatation (panel a) and endothelium-independent dilatation (panel b) before and after 12-months consumption of either an energy-restricted low carbohydrate, high fat diet (LC, n = 26) or a high carbohydrate, low fat diet (LF, n = 23). Values are means  $\pm$  SEM. \*Significant time  $\times$  diet interaction for change in LC compared with LF.

different between the groups at Week 0 (LC:  $20.4 \pm 1.0\%$ , LF:  $19.8 \pm 1.0\%$ ;  $P = 0.64$ ) and did not change significantly in either group following the intervention ( $P = 0.48$ ). In the LC group, changes in FMD correlated with changes in plasma folate ( $r = 0.58$ ,  $P < 0.01$ ).

Pulse wave velocity improved during the intervention in both groups (LC  $10.7 \pm 0.6 \text{ m s}^{-1}$  to  $9.3 \pm 0.3 \text{ m s}^{-1}$ , LF  $11.0 \pm 0.6 \text{ m s}^{-1}$  to  $9.5 \pm 0.5 \text{ m s}^{-1}$ ;  $P < 0.01$  time) with no significant effect of diet ( $P = 0.80$  time  $\times$  diet). AIX did not change in either diet group (LC  $29.6 \pm 2.0\%$  to  $29.7 \pm 2.2\%$ , LF  $27.1 \pm 2.1\%$  to  $28.0 \pm 1.8\%$ ;  $P = 0.80$  time,  $P = 0.16$  time  $\times$  diet).

#### Blood lipids and endothelial function markers

Participants in the LC group had greater increases in total cholesterol and LDL-C ( $P < 0.05$  time  $\times$  diet interaction), Table 2. At 1-year, participants in LC also appeared to have greater reductions in triglycerides and increases in HDL, although these did not reach statistical significance ( $P < 0.07$ ). In LC, changes in LDL did not correlate with changes in FMD ( $r = 0.24$ ,  $P = 0.24$ ).

PAI-1, tPA, and eSelectin were reduced and Adiponectin levels increased in both groups over time ( $P < 0.01$ , time effect) with no diet effect ( $P \geq 0.30$  time  $\times$  diet). VCAM-1 did not change in either group during the intervention ( $P = 0.84$ ). For ICAM-1 a significant time  $\times$  diet interaction was observed ( $P < 0.05$ ) such that ICAM-1 levels decreased to a greater extent in LC compared with LF; however, after controlling for baseline differences this interaction was no longer statistically significant ( $P = 0.14$  time  $\times$  diet). Changes in body weight correlated with changes in: tPA ( $r = 0.54$ ,  $P < 0.001$ ), eSelectin ( $r = 0.31$ ,  $P = 0.03$ ), ICAM-1 ( $r = 0.43$ ,  $P < 0.01$ ) and PAI-1 ( $r = 0.45$ ,  $P < 0.01$ ).

#### Weight loss and blood pressure

At Week 0, there was no difference between treatment groups in body weight (LC  $94.2 \pm 3.2 \text{ kg}$ , LF  $97.5 \pm 2.7 \text{ kg}$ ;  $P = 0.44$ ) or BMI (LC  $33.5 \pm 0.8 \text{ kg m}^{-2}$ , LF  $33.9 \pm 0.8 \text{ kg m}^{-2}$ ;  $P = 0.77$ ). By Week 52, the magnitude of weight loss was similar in both diet groups (LC  $-14.9 \pm 2.1 \text{ kg}$ , LF  $-11.5 \pm 1.5 \text{ kg}$ ;  $P = 0.20$  time  $\times$  diet effect) with an overall mean weight loss of  $13.9\%$ . Reductions in BMI were also similar in both groups (LC  $-5.3 \pm 0.7 \text{ kg m}^{-2}$ , LF  $-3.9 \pm 0.5 \text{ kg m}^{-2}$ ;  $P = 0.14$ ). By 12 months, blood pressure had reduced in both groups (LC  $-14 \pm 2/-6 \pm 2 \text{ mmHg}$ , LF  $-15 \pm 3/-8 \pm 2 \text{ mmHg}$ ;  $P < 0.001$  for time), with no effect of diet ( $P \geq 0.47$  time  $\times$  diet interaction).

#### Plasma B12, Folate and Homocysteine

At Week 0, there were no significant differences between the groups for plasma folate (LC  $22.6 \pm 1.9 \text{ nmol L}^{-1}$ , LF  $21.6 \pm 2.0 \text{ nmol L}^{-1}$ ;  $P = 0.72$ ) or plasma B12 (LC  $272 \pm 19 \text{ pmol L}^{-1}$ , LF  $277 \pm 26 \text{ pmol L}^{-1}$ ;  $P = 0.88$ ). By Week 52, there were significant differential diet effects for these variables such that plasma folate decreased in the LC diet and increased in LF diet (LC  $-4.2 \pm 1.6 \text{ nmol L}^{-1}$ , LF  $6.8 \pm 2.0 \text{ nmol L}^{-1}$ ;  $P < 0.001$  time by diet

**Table 2** Levels of blood lipid and endothelial function markers and adiponectin before and after 12 months consumption of either an energy-restricted low carbohydrate, high fat diet (LC, n = 26) or a high carbohydrate, low fat diet (LF, n = 23)

Variable	Diet	Week 0	Week 52	Change	Mean difference	95% CI Lower	95% CI Upper	Time × diet P-value
<b>Lipids</b>								
Total cholesterol (mmol L <sup>-1</sup> )	LC	5.40 ± 0.16	6.00 ± 0.27*	0.61 ± 0.24	0.59	0.01	1.16	<0.05
	LF	5.59 ± 0.16	5.60 ± 0.21	0.02 ± 0.15				
HDL-C (mmol L <sup>-1</sup> )	LC	1.41 ± 0.05	1.69 ± 0.10**	0.28 ± 0.08	0.20	-0.02	0.42	0.07
	LF	1.36 ± 0.05	1.43 ± 0.07**	0.08 ± 0.08				
Triglycerides (mmol L <sup>-1</sup> )	LC	1.70 ± 0.14	1.13 ± 0.13***	-0.57 ± 0.12	-0.33	-0.71	0.04	0.06
	LF	1.65 ± 0.14	1.41 ± 0.21***	-0.24 ± 0.15				
LDL-C (mmol L <sup>-1</sup> )	LC	3.22 ± 0.16	3.82 ± 0.25*	0.60 ± 0.22	0.58	0.08	1.08	0.03
	LF	3.46 ± 0.15	3.48 ± 0.16	0.02 ± 0.10				
Plasma glucose (mmol L <sup>-1</sup> )	LC	5.55 ± 0.09	5.33 ± 0.09***	0.21 ± 0.07	0.08	-0.15	0.30	0.49
	LF	5.56 ± 0.13	5.27 ± 0.10***	0.29 ± 0.09				
<b>Endothelial function</b>								
tPA (ng mL <sup>-1</sup> )	LC	4.2 ± 0.3	2.9 ± 0.4***	-1.2 ± 0.3	-0.2	-1.0	0.6	0.61
	LF	4.1 ± 0.4	3.0 ± 0.4***	-1.0 ± 0.3				
PAI-1 (ng mL <sup>-1</sup> )	LC	72.7 ± 3.3	62.3 ± 3.8**	-10.4 ± 3.9	-3.9	-13.8	6.0	0.43
	LF	68.0 ± 2.4	61.5 ± 3.1**	-6.5 ± 2.8				
eSelectin (ng mL <sup>-1</sup> )	LC	30.3 ± 2.5	26.5 ± 2.6***	-3.8 ± 1.0	-0.4	-3.6	2.8	0.79
	LF	28.5 ± 1.5	25.2 ± 1.3***	-3.3 ± 1.3				
VCAM-1 (ng mL <sup>-1</sup> )	LC	976.4 ± 36.7	954.6 ± 40.1	-21.7 ± 37.9	-31.2	-151.4	88.9	0.60
	LF	968.0 ± 37.8	977.6 ± 40.8	9.5 ± 46.7				
ICAM-1 (ng mL <sup>-1</sup> )	LC	117.5 ± 6.5	100.0 ± 5.5**	-17.5 ± 4.6	-12.4	-24.5	-0.3	<0.05
	LF	105.3 ± 5.7	100.1 ± 5.2	-5.1 ± 3.7				
Adiponectin (μg mL <sup>-1</sup> )	LC	15.7 ± 1.2	18.5 ± 1.3***	2.8 ± 0.8	-1.8	-5.2	1.6	0.30
	LF	15.4 ± 1.0	20.0 ± 2.0***	4.6 ± 1.6				

LC, low carbohydrate diet group; LF, low fat diet group; HDL-C, high-density lipoprotein cholesterol; ICAM-1, intercellular adhesion molecule-1; LDL-C, low-density lipoprotein cholesterol; PAI-1, plasminogen activator inhibitor-1; tPA, tissue plasminogen activator; VCAM-1, vascular cell adhesion molecule-1. All values are mean ± SEM. \*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001 compared to week 0.

interaction), whilst for plasma B12 levels increased in the LC diet ( $113 \pm 41 \text{ pmol L}^{-1}$ ) but remained unchanged in the LF diet ( $7 \pm 16 \text{ pmol L}^{-1}$ ).

At baseline, the LC group had lower plasma homocysteine levels compared with LF that approached conventional statistical significance ( $P = 0.16$ ). Plasma homocysteine increased in both treatment groups during the intervention (LC  $5.9 \pm 0.3 \mu\text{mol L}^{-1}$  to  $7.9 \pm 0.3 \mu\text{mol L}^{-1}$ , LF  $6.6 \pm 0.3 \mu\text{mol L}^{-1}$  to  $7.8 \pm 0.4 \mu\text{mol L}^{-1}$ ;  $P < 0.001$ ); with a significant effect of diet as a result of a greater increase in LC compared with LF (LC  $1.9 \pm 0.2 \mu\text{mol L}^{-1}$ , LF  $1.3 \pm 0.2 \mu\text{mol L}^{-1}$ ;  $P = 0.04$  time × diet interaction). After adjusting

for baseline differences the time × diet interaction was no longer significant ( $P = 0.09$ ). There was a significant correlation between the changes in plasma homocysteine and plasma folate ( $r = -0.44$ ,  $P < 0.01$ ).

## Discussion

The main findings of the present study were that both LC and LF hypoenergetic diets achieved similar reductions in body weight and were associated with improvements in PWV and a number of endothelium-derived factors. However, the LC diet impaired FMD suggesting chronic consumption of a

LC diet may have detrimental effects on endothelial function.

Consistent with other studies [9] greater decreases in triglycerides and increases in HDL-C, total cholesterol and LDL-C were observed in the LC group relative to the LF group. Although, conventional significance was not reached for the differential changes between the diets for HDL-C and triglycerides this may reflect lower statistical power within the sub-sample of participants in this study given that a similar magnitude of change that reached statistical significance was evident in the larger study cohort [7].

In the current study, we have extended the evaluation of effects of LC and LF diets on CVD risk beyond blood lipids and other traditional metabolic risk markers to assess markers of endothelial function. Brachial artery FMD is a marker of endothelial function [31] that is correlated with coronary artery dilatory function and is an independent predictor of future cardiac events [35]. We observed a significant effect of diet composition at 12-months with FMD remaining unchanged in LF group, but impaired in the LC group. A reduction in FMD of the ~2% (absolute) magnitude observed in the LC diet group has previously been associated with a clinically relevant elevation in CVD risk [21]. A recent prospective study reported that in a patient group similar to that in the present study an FMD response  $\leq 4.5\%$  was associated with a significantly greater risk of suffering a CV event [21], suggesting that the ~2% reduction in FMD observed in the LC group may have important implications for future cardiac events. However, the sample size of the study was relatively small and larger studies are required to confirm this effect.

As there was no change in endothelial-independent dilatation (i.e. glyceryl-trinitrate stimulated) in either diet group the reduction in FMD in the LC group was most likely because of an impairment of endothelial nitric oxide production which may have occurred as a result of endothelial damage [36]. Although the exact mechanism for the present effect is difficult to explain, previous studies have suggested that high levels of LDL-C are associated with reduced FMD [37]. However, despite increased LDL-C with the LC diet, there was no relationship between the changes in LDL-C and FMD, suggesting that the rise in LDL-C may not have mediated this effect, although this cannot be entirely dismissed. Apart from LDL-C other factors are known to affect FMD [35], with previous studies demonstrating improvements with folate supplementation [38, 39]. We observed a significant

inverse relationship between the change in FMD and change in folate with the LC group, suggesting the reduction in plasma folate in the LC diet may have contributed to the impairment in FMD. However, the plasma folate may only be serving as a good marker for a reduction in fruit and vegetables in the LC diet as the absolute changes are small. A previous study [15] observed no changes in FMD after 52 weeks of consuming a low carbohydrate, low saturated fat diet, which suggests the higher saturated fat content of the LC diet used in the present study, independent of changes in blood lipids may also play a role in the impairment in FMD. The level of carbohydrate content used in that study was also considerably higher ( $\sim 140 \text{ g day}^{-1}$  vs.  $20\text{--}40 \text{ g day}^{-1}$ ), so whether the high degree of carbohydrate restriction also contributed to the effects observed remains unclear. It has also been previously shown that dietary patterns adequate in fruit, vegetable, nuts, whole grains and olive oil is protective of endothelial function [40], which may provide an alternative explanation for the impairment in FMD observed with the LC diet. It is therefore evident that greater examination of these factors as well as other factors that are known to influence FMD (e.g. oxidative stress and nitric oxide bioavailability [35]) is required to elucidate the mechanisms responsible for the observed effect.

Pulse wave velocity is an indirect measure of aortic stiffness, with a faster PWV indicating a stiffer aorta. Consistent with previous studies PWV was reduced with weight loss [41, 42]. The magnitude of the response was comparable in both diet groups. A reduction in pulse wave velocity is associated with improved arterial compliance and decreased CVD risk [43]. In contrast, AIx, a measure of systemic arterial stiffness derived from the ascending aortic pressure waveform, did not change in either group. Although both PWV and AIx are indicators of cardiovascular stiffness, this data suggests they may not be under the same mechanistic control or these diet effects are limited to peripheral rather than central arterial effects and further clarification is required.

Consistent with previous studies [15, 16, 19], improvements in a number of vascular health markers, including adiponectin, fibrinolytic factors and several cellular adhesion molecules occurred following weight loss, independent of diet composition. It has been proposed that adiponectin may be responsible for mediating reductions in CVD risk associated with weight loss by modulating the endothelial inflammatory response [44]. Ouchi *et al.* [44] showed that adiponectin inhibits expression of VCAM-1,

ICAM-1 and eSelectin in a dose-dependant manner. In the current study, we also observed a correlation between the changes in adiponectin and VCAM-1 ( $r = 0.47$ ,  $P < 0.001$ ). For ICAM-1, a significant time by diet interaction was observed such that greater relative reductions occurred in LC compared with LF; however, after controlling for baseline differences this interaction was no longer significant, suggesting the greater reductions observed in the LC group may have been associated with higher baseline levels. These reductions in a number of systemic endothelium-derived factors and PWV with weight loss, independent of diet composition, occurred somewhat in a paradoxical fashion to the FMD response that did not improve after weight loss and decreased following the LC diet. In agreement, a previous study also showed improvements in a number of endothelium-derived and PWV following weight loss (6.3 kg), with no change in FMD. The reason for these differing effects is not clear, but suggests these markers of endothelial function are regulated by alternate independent mechanisms. Koybayashi *et al.* [45] indicated that brachial FMD and PWV evaluate different aspects of atherosclerosis as well as different sites of the artery. Nevertheless, both have been shown to be good surrogate markers of clinical atherosclerosis and their combination maybe of strong clinical relevance [45]. Additionally, PAI-1, tPa and adiponectin also appear to be an independent predictors of myocardial infarction [12, 46, 47]. Hence, based on the varying responses between endothelium-derived factors, PWV and FMD the long-term effects of weight loss following either a LC or LF diets on future cardiac events needs further clarification. Recently, Shai *et al.* [8] showed no detrimental effect of a LC diet on CVD risk after 2 years. However, the LC diet consumed in that study was substantially higher in carbohydrate and lower in total fat and saturated fat in comparison to the current study.

Elevated homocysteine has been identified as an independent CVD risk factor [48]. Plasma folate and B12 are involved in the metabolic pathway of homocysteine and deficiencies in these micronutrients have been associated with elevated homocysteine levels [49]. In the present study, plasma folate increased in the LF diet group but was reduced in the LC diet group, which most likely reflected the relative changes in consumption of folate rich foods, including fruit, vegetables and fortified breads and cereal foods [50]. Conversely, participants in the LC diet group experienced greater increases in plasma B12 that could be attributed to a larger relative increased consumption of animal products [50]. In the

LC group, a greater elevation in homocysteine was observed and the inverse relationship between changes in plasma folate and homocysteine suggests the greater reductions in folate also observed in this group may have been responsible for this effect. Nevertheless, despite the increases in homocysteine, levels remained within the normal recommended range ( $<10 \mu\text{mol L}^{-1}$ ) for both diet groups [49] suggesting the observed rises may not be of clinical significance.

In conclusion, both LC and LF hypoenergetic diets achieved similar reductions in body weight and were associated with improvements in PWV and a number of endothelium-derived factors. However, the LC diet impaired FMD suggesting chronic consumption of a LC diet may have detrimental effects on endothelial function. Whether this adversely affects clinical endpoints remains unknown and further larger, longer term studies are required.

#### Acknowledgments

We thank the volunteers who made the study possible through their participation. We gratefully acknowledge Kathryn Bastiaans, Julia Weaver and Anne McGuffin, and Vanessa Courage for coordinating this trial; Xenia Cleanthous, Julianne McKeough and Gemma Williams for assisting in delivering the dietary intervention; Rosemary McArthur and Lindy Lawson for nursing expertise; Candita Sullivan, Julie Turner, Cathryn Seccafin, Vanessa Russell and Mark Mano for assisting with the biochemical assays and Julie Syrette for assisting with data management.

#### Funding/Support

This study was supported by project grants from the National Heart Foundation of Australia and the National Health and Medical Research Council of Australia. Simplot Australia, Mt Buffalo Hazelnuts Victoria, Webster Walnuts Victoria, Stahmann Farms Queensland and Scalzo Food Industries Victoria donated foods for this study. None of the funding agencies played a role in the conception, design or conduct of the study, collection, management, analysis and interpretation of the data; or preparation, review, and approval of the manuscript.

#### Disclosures

None of the authors had a conflict of interest in relation to this manuscript.

## References

- Lichtenstein AH, Appel LJ, Brands M *et al*. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation* 2006; **114**: 82–96.
- Hession M, Rolland C, Kulkarni U, Wise A, Broom J. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. *Obes Rev* 2009; **10**: 36–50.
- Kromhout D, Menotti A, Bloemberg B *et al*. Dietary saturated and trans fatty acids and cholesterol and 25-year mortality from coronary heart disease: the Seven Countries Study. *Prev Med* 1995; **24**: 308–15.
- Foster GD, Wyatt HR, Hill JO *et al*. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* 2003; **348**: 2082–90.
- Samaha FF, Iqbal N, Seshadri P *et al*. A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* 2003; **348**: 2074–81.
- Gardner CD, Kiazand A, Alhassan S *et al*. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A TO Z Weight Loss Study: a randomized trial. *JAMA* 2007; **297**: 969–77.
- Brinkworth GD, Noakes M, Buckley JD, Keogh JB, Clifton PM. Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. *Am J Clin Nutr* 2009; **90**: 23–32.
- Shai I, Schwarzfuchs D, Henkin Y *et al*. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* 2008; **359**: 229–41.
- Nordmann AJ, Nordmann A, Briel M *et al*. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; **166**: 285–93.
- Braunwald E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997; **337**: 1360–9.
- Hope SA, Meredith IT. Cellular adhesion molecules and cardiovascular disease. Part I. Their expression and role in atherogenesis. *Int Med J* 2003; **33**: 380–6.
- Thogersen AM, Jansson JH, Boman K *et al*. High plasminogen activator inhibitor and tissue plasminogen activator levels in plasma precede a first acute myocardial infarction in both men and women: evidence for the fibrinolytic system as an independent primary risk factor. *Circulation* 1998; **98**: 2241–7.
- Smith FB, Lee AJ, Rumley A, Fowkes FG, Lowe GD. Tissue-plasminogen activator, plasminogen activator inhibitor and risk of peripheral arterial disease. *Atherosclerosis* 1995; **115**: 35–43.
- Arita Y, Kihara S, Ouchi N *et al*. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999; **257**: 79–83.
- Keogh JB, Brinkworth GD, Clifton PM. Effects of weight loss on a low-carbohydrate diet on flow-mediated dilatation, adhesion molecules and adiponectin. *Br J Nutr* 2007; **98**: 852–9.
- Sharman MJ, Volek JS. Weight loss leads to reductions in inflammatory biomarkers after a very-low-carbohydrate diet and a low-fat diet in overweight men. *Clin Sci (Lond)* 2004; **107**: 365–9.
- Murakami T, Horigome H, Tanaka K *et al*. Impact of weight reduction on production of platelet-derived microparticles and fibrinolytic parameters in obesity. *Thromb Res* 2007; **119**: 45–53.
- Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. *Endocr Rev* 2005; **26**: 439–51.
- Keogh JB, Brinkworth GD, Noakes M, Belobajdic DP, Buckley JD, Clifton PM. Effects of weight loss from a very-low-carbohydrate diet on endothelial function and markers of cardiovascular disease risk in subjects with abdominal obesity. *Am J Clin Nutr* 2008; **87**: 567–76.
- Hashimoto M, Akishita M, Eto M *et al*. The impairment of flow-mediated vasodilatation in obese men with visceral fat accumulation. *Int J Obes Relat Metab Disord* 1998; **22**: 477–84.
- Rossi R, Nuzzo A, Origliani G, Modena MG. Prognostic role of flow-mediated dilation and cardiac risk factors in post-menopausal women. *J Am Coll Cardiol* 2008; **51**: 997–1002.
- Vogel RA, Corretti MC, Plotnick GD. Effect of a single high-fat meal on endothelial function in healthy subjects. *Am J Cardiol* 1997; **79**: 350–4.
- Tentolouris N, Arapostathi C, Perrea D, Kyriaki D, Revenas C, Katsilambros N. Differential effects of two isoenergetic meals rich in saturated or monounsaturated fat on endothelial function in subjects with type 2 diabetes. *Diabetes Care* 2008; **31**: 2276–8.
- Keogh JB, Grieger JA, Noakes M, Clifton PM. Flow-mediated dilatation is impaired by a high-saturated fat diet but not by a high-carbohydrate diet. *Arterioscler Thromb Vasc Biol* 2005; **25**: 1274–9.
- Miller M, Beach V, Sorkin JD *et al*. Comparative effects of three popular diets on lipids, endothelial function, and C-reactive protein during weight maintenance. *J Am Diet Assoc* 2009; **109**: 713–7.
- Fuentes F, Lopez-Miranda J, Sanchez E *et al*. Mediterranean and low-fat diets improve endothelial function in hypercholesterolemia men. *Ann Intern Med* 2001; **134**: 1115–9.
- Rallidis LS, Lekakis J, Kolomvotsou A *et al*. Close adherence to a Mediterranean diet improves endothelial function in subjects with abdominal obesity. *Am J Clin Nutr* 2009; **90**: 263–8.
- Phillips SA, Jurva JW, Syed AQ *et al*. Benefit of low-fat over low-carbohydrate diet on endothelial health in obesity. *Hypertension* 2008; **51**: 376–82.
- Buscemi S, Verga S, Tranchina MR, Cottone S, Cerasola G. Effects of hypocaloric very-low-carbohydrate diet vs. Mediterranean diet on endothelial function in obese women\*. *Eur J Clin Invest* 2009; **39**: 339–47.
- Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new worldwide definition. A Consensus Statement from the International Federation. *Diabet Med* 2006; **23**: 469–80.
- Corretti MC, Anderson TJ, Benjamin EJ *et al*. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002; **39**: 257–65.
- Jarvisalo MJ, Jartti L, Karvonen MK *et al*. Enhanced endothelium-dependent vasodilation in subjects with Proline7 substitution in the signal peptide of neuropeptide Y. *Atherosclerosis* 2003; **167**: 319–26.
- Eskurza I, Monahan KD, Robinson JA, Seals DR. Effect of acute and chronic ascorbic acid on flow-mediated dilatation with sedentary and physically active human ageing. *J Physiol* 2004; **556**: 315–24.
- Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18**: 499–502.

- 35 Raitakari OT, Celermajer DS. Flow-mediated dilatation. *Br J Clin Pharmacol* 2000; **50**: 397–404.
- 36 Joannides R, Haeveli WE, Linder L *et al*. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries *in vivo*. *Circulation* 1995; **91**: 1314–9.
- 37 Kuvvin JT, Patel AR, Sliney KA, Pandian NG, Karas RH. Comparison of flow-mediated dilatation of the brachial artery in coronary patients with low-density lipoprotein cholesterol levels 80 mg/dl versus patients with levels <80 to 100 mg/dl. *Am J Cardiol* 2005; **95**: 93–5.
- 38 Woo KS, Chook P, Chan LL *et al*. Long-term improvement in homocysteine levels and arterial endothelial function after 1-year folic acid supplementation. *Am J Med* 2002; **112**: 535–9.
- 39 Woo KS, Chook P, Lolin YI, Sanderson JE, Metreweli C, Celermajer DS. Folic acid improves arterial endothelial function in adults with hyperhomocystinemia. *J Am Coll Cardiol* 1999; **34**: 2002–6.
- 40 Espósito K, Marfella R, Cirola M *et al*. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA* 2004; **292**: 1440–6.
- 41 Clifton PM, Keogh JB, Foster PR, Noakes M. Effect of weight loss on inflammatory and endothelial markers and FMD using two low-fat diets. *Int J Obes (Lond)* 2005; **29**: 1445–51.
- 42 Toto-Moukouo JJ, Achimastos A, Asmar RG, Hugues CJ, Safar ME. Pulse wave velocity in patients with obesity and hypertension. *Am Heart J* 1986; **112**: 136–40.
- 43 Boutouyrie P, Tropeano AI, Asmar R *et al*. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. *Hypertension* 2002; **39**: 10–5.
- 44 Ouchi N, Kihara S, Arita Y *et al*. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation* 1999; **100**: 2473–6.
- 45 Kobayashi K, Akishita M, Yu W, Hashimoto M, Ohni M, Toba K. Interrelationship between non-invasive measurements of atherosclerosis: flow-mediated dilation of brachial artery, carotid intima-media thickness and pulse wave velocity. *Atherosclerosis* 2004; **173**: 13–8.
- 46 Cushman M, Lemaitre RN, Kuller LH *et al*. Fibrinolytic activation markers predict myocardial infarction in the elderly. The Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol* 1999; **19**: 493–8.
- 47 Pischedda T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA* 2004; **291**: 1730–7.
- 48 Selhub J. The many facets of hyperhomocysteinemia: studies from the Framingham cohorts. *J Nutr* 2006; **136**: 1726S–30S.
- 49 Malinow MR, Boston AG, Krauss RM. Homocyst(e)ine, diet, and cardiovascular diseases: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation* 1999; **99**: 178–82.
- 50 Allen LH. Causes of vitamin B12 and folate deficiency. *Food Nutr Bull* 2008; **29**: S20–34.

*Correspondence:* Dr Grant D Brinkworth, CSIRO – Human Nutrition, PO Box 10041 BC, Adelaide, South Australia 5000, Australia.  
(fax: +61 8 8303 8899; e-mail: grant.brinkworth@csiro.au).

Trial Registration: Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au>) ACTR No: 12606000203550. ■