Beyond Energy Balance: Physiologic Mechanisms and Clinical Trial Evidence for Ketogenic Diets

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Re-Evaluating the Paradigm: Substrates over Calories

Metabolic Adaptation to weight loss- Famine or diet?

- Hunger (Leptin/Ghrelin, suppressed CCK/PYY)
- Cravings and food reward circuits
- RMR
- REE
- NEAT
- Thyroid

Almost Any Diet Can Be Keto



Defining Low Carb

Generic low Carb

<130g/day

Very low carb/ketogenic

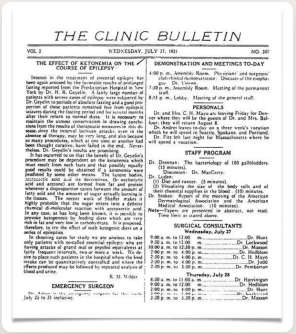
<50g/day total or 30g net

In reality, it's all about the ketones

Modern "Keto Diet"

0-5% Carbs 20-30% protein 65-80% fat

Not A New Intervention



THE CLINIC BULLETIN

VOL. 2 WEDNESDAY, JULY 27, 1921 NO. 167

THE EFFECT OF KETONEMIA ON THE COURSE OF EPILEPSY

DEMONSTRATION AND MEETINGS TO-DAY

PERSONALS

STAFF PROGRAM

SURGICAL CONSULTANTS

EMERGENCY SURGEON

Nutritional Ketosis vs DKA

DKA	Nutritional Ketosis
Life threatening condition with inadequate insulin	Natural physiologic process from burning fatty acids for energy
Elevated blood glucose (usually)	Normal Blood glucose
Signs of acidosis with pH, bicarb, CO2	Normal pH, bicarb, CO2
Ketones >3.5 but often above 10	Ketones usually 0.5-3, but can be higher
Ill, usually a trigger, feel bad, nausea, vomiting, trouble breathing	Feel well

BMJ Nutr Prev Health. 2023 Jan 2;6(1):46-55. doi: 10.1136/bmjnph-2022-000544. eCollection 2023.

What predicts drug-free type 2 diabetes remission? Insights from an 8-year general practice service evaluation of a lower carbohydrate diet with weight loss

David Unwin [1 2], Christine Delon [1 3], Jen Unwin [4], Simon Tobin [4], Roy Taylor [5]

Affiliations + expand

PMID: 37559961 PMCID: PMC10407412 DOI: 10.1136/bmjnph-2022-000544

Abstract

Diabetes Ther (2018) 9:583–612
https://doi.org/10.1007/s13300-018-0373-9

CrossMark

ORIGINAL RESEARCH

Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study

Sarah J. Hallberg · Amy L. McKenzie · Paul T. Williams · Nasir H. Bhanpuri · Anne L. Peters · Wayne W. Campbell · Tamara L. Hazbun · Brittanie M. Volk · James P. McCarter · Stephen D. Phinney · Jeff S. Volek

Received: December 28, 2017 / Published online: February 7, 2018
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Real-World Low-Carb Intervention Results (Norwood Surgery)

Cohort Size
n=186
(39% of T2D Register) over 33 months (median)

Weight Loss
-10 kg
(mean) | fell from 97 to 86 kg (median)

HbA1c Reduction
fell from
63 to 46 mmol/mol
(median)

Diabetes Remission
51%
overall (77% if T2D duration < 1 year)

Cardiometabolic Improvements

LDL-C	Triglycerides	Systolic BP
-0.5 mmol/L	-0.9 mmol/L	-12 mmHg

Prescribing Savings Norwood Surgery spent £68,353 less per year than the area average

Source: Unwin D et al. BMJ Nutr Prev Health. 2023;6(1):46–55. doi:10.1136/bmjnph-2022-000544. Eight-year general practice service evaluation.

1-Year Continuous Care Intervention (CCI) Results

Enrolled at 1 Year:
83%

HbA1c Reduction:	7.6% to 6.3%
Weight Decline:	13.8 kg
T2D Medication (Non-Metformin) Declined from	56.9% to 29.7%
Insulin Therapy:	Reduced or eliminated in 94% of users
Sulfonylureas:	100% eliminated

Source: Hallberg SJ et al. Diabetes Ther. 2018;9:583–612. doi:10.1007/s13300-018-0373-9. Open-label, non-randomized, controlled study.

Physiologic Mechanisms

Reduce Insulin/Glucagon ratio

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- Reduce Insulin/Glucagon ratio
- **Suppress hepatic DNL**

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- Reduce Insulin/Glucagon ratio
- Suppress hepatic DNL
- Ketone HDAC inhibitor
- Inhibits NLRP3 inflammasome
- **Suppress ghrelin, increase PYY CCK**

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- Suppress hepatic DNL
- Ketone HDAC inhibitor
- Inhibits NLRP3 inflammasome
- Suppress ghrelin, increase PYY CCK
- **"Alternate" fuel source**

Physiologic Mechanisms

- Reduce Insulin/Glucagon ratio
- Suppress hepatic DNL
- Ketone HDAC inhibitor
- **Inhibits NLRP3 inflammasome**

Clinical Trials

Meta-Analysis > Nutr Rev. 2022 Feb 10;80(3):488-502. doi: 10.1093/nutrit/nuab040.

Effect of a very low-carbohydrate ketogenic diet vs recommended diets in patients with type 2 diabetes: a meta-analysis

Mohamed Rafiullah [1], Mohthash Musambil [1], Satish Kumar David [1]

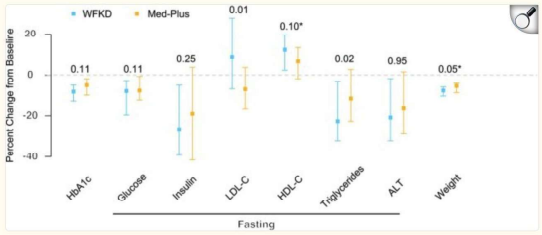
Affiliations + expand

PMID: 34338787 DOI: 10.1093/nutrit/nuab040

Objective: This meta-analysis compares the effect of a VLCK diet on glycemic control, body weight, lipid profile, medication use, and dropouts with that of recommended diets for 12 weeks or longer in people with type 2 diabetes.

Results: Compared with control diets, the VLCK diet resulted in a greater decrease in hemoglobin A1c after 3 months (weighted mean difference[WMD]: -6.7 mmol/mol; 95%CI, -9.0 to -4.4) (WMD: -0.61%; 95%CI, -0.82 to -0.40; P < 0.001; moderate-certainty evidence) and after 6 months (WMD: -6.3 mmol/mol; 95%CI, -9.3 to -3.5) (WMD: -0.58%; 95%CI, -0.85 to -0.32; low-certainty evidence). There was a significantly greater weight loss with the VLCK diet after 3 months (WMD: -2.91 kg; 95%CI, -4.88 to -0.95; low-certainty evidence) and after 6 months (WMD: -2.84 kg; 95%CI, -5.29 to -0.39; low-certainty evidence). The VLCK diet was not better than a control diet after 12 months. It was superior in decreasing triglyceride levels, increasing high-density lipoprote cholesterol levels, and reducing the use of antidiabetic medications for up to 12 months.

FIGURE 3.



Am J Clin Nutr. 2022 May 31;116(3):640–652. doi: 10.1093/ajcn/nqac154

Effect of a ketogenic diet versus Mediterranean diet on glycated hemoglobin in individuals with prediabetes and type 2 diabetes mellitus: The interventional Keto-Med randomized crossover trial

Christopher D Gardner [1,*], Matthew J Landry [2], Dalia Perelman [3], Christina Petlura [4], Lindsay R Durand [5], Lucia Aronica [6], Anthony Crimarco [7], Kristen M Cunanan [8], Annie Chang [9], Christopher C Dant [10], Jennifer L Robinson [11], Sun H Kim [12]

Conclusions

HbA1c values were not different between diet phases after 12 weeks, but improved from baseline on both diets, likely due to several shared dietary aspects. The WFKD led to a greater decrease in triglycerides, but also had potential untoward risks from elevated LDL cholesterol and lower nutrient intakes from avoiding legumes, fruits, and whole, intact grains, as well as being less sustainable. This trial was registered at clinicaltrials.gov as NCT03810378.

Methods

Keto-Med was a randomized, crossover, interventional trial. Forty participants aged ≥18 years with prediabetes or T2DM followed the well-formulated ketogenic diet (WFKD) and the Mediterranean-plus diet (Med-Plus) for 12 weeks each, in random order. The diets shared the 3 key similarities noted above. The Med-Plus incorporated legumes, fruits, and whole, intact grains, while the WFKD avoided them. The primary outcome was the percentage change in glycated hemoglobin (HbA1c) after 12 weeks on each diet. Secondary and exploratory outcomes included percentage changes in body weight, fasting insulin, glucose, and blood lipids; average glucose from continuous glucose monitor (CGM), and nutrient intake.

Antihyperglycemic medications

To minimize the risk of hypoglycemia, individuals with T2DM were instructed to stop sulfonylurea medications before starting the WFKD and to reduce the dose by 50% before starting the Med-Plus. Sulfonylurea medications were restarted or increased for persistent hyperglycemia (>180 mg/dL).

the Med-Plus. In sensitivity analyses addressing changes in medications or looking at only the first phase of the crossover, differences between diets for HbA1c and HDL cholesterol values shifted to statistical significance, favoring the WFKD. The dietary adherence assessment indicated similar levels of average adherence between the 2 diets during both the food-delivery period and self-provided period. Differences in nutrient intakes during the

Keto is “better” in short term - Why?

Lower carbs, lower glucose spikes, allows IR to “heal”

Helps clear liver and visceral fat

Supplemental Table 13. Absolute Change [Mean (95% Confidence Interval)] in Primary and Secondary Outcomes by Diet Order and Phase, with Tests of Interaction

Outcome	Diet Order	Phase 1 (n)	Phase 2 (n)	Baseline	End of Phase 1 (12 wk)	End of Phase 2 (12 wk)
Primary outcome						
HbA1c (%)	WFKD to Med-Plus	16	17	6.28 (5.93,6.62)	5.63(5.34,5.92)	5.72(5.4,6.05)
	Med-Plus to WFKD	17	16	6.12 (5.84,6.41)	5.81(5.53,6.08)	5.71(5.51,5.91)
Secondary outcomes						
Fasting Glucose (mg/dL)	WFKD to Med-Plus	16	17	121.6 (113.2, 130.0)	108.6 (97.8, 119.4)	117.6 (95.4, 139.7)
	Med-Plus to WFKD	17	16	121.8 (110.1, 133.4)	113.3 (100.7, 125.9)	107.8 (93.4, 122.3)
Fasting Insulin (µU/mL)	WFKD to Med-Plus	16	17	17.8 (13.9, 21.8)	13.1 (10.0, 16.3)	20.4 (6.7, 34.0)
	Med-Plus to WFKD	17	16	18.7 (10.9, 26.4)	15.5 (9.5, 21.6)	12.6 (10.1, 15.2)
Fasting LDL-C (mg/dL)	WFKD to Med-Plus	16	17	97.8 (85.8, 109.9)	111.3 (91.1, 131.4)	97.8 (84.7, 110.8)
	Med-Plus to WFKD	17	16	111.5 (96.8, 126.3)	95.3 (81.1, 109.5)	117.2 (86.9, 147.5)
Fasting HDL-C (mg/dL)	WFKD to Med-Plus	16	17	49.1 (43.2, 55.0)	54.1 (47.5, 60.7)	55.9 (48.6, 63.3)
	Med-Plus to WFKD	17	16	48.0 (43.0, 53.1)	47.9 (43.7, 53.1)	53.7 (47.7, 59.7)
Fasting Triglycerides (mg/dL)	WFKD to Med-Plus	16	17	118.8 (92.5, 145.1)	99.5 (80.8, 118.2)	111.8 (88.8, 134.9)
	Med-Plus to WFKD	17	16	131.1 (94.9, 167.3)	121.7 (74.5, 168.8)	93.3 (77.9, 108.7)
Fasting ALT (IU/L)	WFKD to Med-Plus	16	17	28.4 (22.4, 34.5)	24.9 (19.5, 30.3)	24.5 (18.2, 30.8)
	Med-Plus to WFKD	17	16	27.7 (22.0, 33.4)	22.6 (19.0, 26.1)	21.2 (16.7, 23.6)
Weight (kg)	WFKD to Med-Plus	16	17	90.1 (83.0, 97.1)	81.7 (73.3, 89.5)	81.3 (75.4, 87.3)
	Med-Plus to WFKD	17	16	85.6 (78.2, 93.0)	80.8 (73.2, 88.4)	79.3 (72.6, 86.0)
Exploratory outcome[1]						
Avg CGM (mg/dL)	WFKD to Med-Plus	18	17	125.3 (117.3, 141.4)	119.5 (109.2, 125.5)	123.8 (114.5, 138.8)
	Med-Plus to WFKD	17	18	128.9 (115.8, 142.0)	122.6 (113.9, 131.2)	115.5 (103.8, 127.2)

[1]Continuous Glucose Monitor (CGM) metrics proved to be unexpectedly valuable when the pandemic prevented two participants who completed the trial from providing HbA1c values; the CGM data were obtained remotely for all participants who completed the trial.
Abbreviations: WFKD, Whole Food-based Ketogenic Diet; Med-Plus, Mediterranean-Plus; HbA1c, Glycosylated Hemoglobin; CGM, Continuous Glucose Monitor; LDL-C, Low Density Lipoprotein Cholesterol; HDL-C, High Density Lipoprotein Cholesterol; ALT, Alanine Aminotransferase

Keto is “better” in short term - Why?

Lower carbs, lower glucose spikes, allows IR to “heal”

Helps clear liver and visceral fat

Deprescribe insulin and insulin secretagogues

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- Lower carbs, lower glucose spikes, allows IR to “heal”
- Helps clear liver and visceral fat
- Deprescribe insulin and insulin secretagogues
- Reduced hunger despite weight loss
- **Eat less and lose more weight**

Summary

The influence of diet macronutrient content on the cardiometabolic effects of weight loss in people with metabolically unhealthy obesity (prediabetes and hepatic steatosis) has important clinical implications. We evaluated the cardiometabolic effects of moderate (~10%) weight loss induced by three popular diets with markedly different macronutrient composition (very-low-carbohydrate ketogenic, Mediterranean, and very-low-fat plant-forward). Weight loss increased muscle insulin sensitivity by ~50% in all groups but caused a two-to-three-fold greater increase in hepatic insulin sensitivity in the very-low-carbohydrate group than the other groups ($p < 0.001$). Intrahepatic triglyceride content, hepatic *de novo* lipogenesis, glycated hemoglobin, and 24-h serial plasma glucose and insulin decreased most in the very-low-carbohydrate group. There were no differences among groups in LDL-cholesterol, apolipoprotein B, or 24-h plasma triglyceride concentrations. These results demonstrate that a very low carbohydrate diet has greater cardiometabolic benefits, particularly in hepatic metabolic function, than matched 10% weight loss induced by a Mediterranean or very-low-fat diet in people with metabolically unhealthy obesity. This study was registered at ClinicalTrials.gov (NCT02706262).

Keto is “better” in short term - Why?

- Lower carbs, lower glucose spikes, allows IR to “heal”
- Helps clear liver and visceral fat
- Deprescribe insulin and insulin secretagogues
- Reduced hunger despite weight loss
- Eat less and lose more weight
- **Possible less reduction in RMR and better lean mass preservation**

Cardiometabolic Effects of 10% Weight Loss: Ketogenic vs. Med & Very-Low-Fat

1

Superior Hepatic Insulin Sensitivity

Muscle insulin sensitivity increased by ~50% in all groups, but the very-low-carbohydrate ketogenic diet caused a 2-to-3-fold greater increase in hepatic insulin sensitivity ($p < 0.001$).

2

Greatest Reduction in Liver Fat & Glycemia

Intrahepatic triglyceride content, hepatic de novo lipogenesis, glycated hemoglobin (HbA1c), and 24-h serial plasma glucose and insulin decreased most in the very-low-carbohydrate group.

3

Neutral Impact on Lipids & Triglycerides

No differences were observed among the three groups in LDL-cholesterol, apolipoprotein B, or 24-h plasma triglyceride concentrations.

Source: Petersen MC et al. Cell Metab. Online August 27, 2026. NCT02706262. Study population: people with metabolically unhealthy obesity (prediabetes and hepatic steatosis).





After 12% (within 2%) weight loss on a run-in diet, participants were randomly assigned to one of three test diets according to carbohydrate content (high, 60%, n=54; moderate, 40%, n=53; or low, 20%, n=57) for 20 weeks. Test diets were controlled for protein and were energy adjusted to maintain weight loss within 2 kg. To test for effect modification predicted by the carbohydrate-insulin model, the sample was divided into thirds of pre-weight loss insulin secretion (insulin concentration 30 minutes after oral glucose).

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Article

The impact of a ketogenic diet on weight loss, metabolism, body composition and quality of life

Simon Hirschberger [1 2 4], David Effinger [1 2 4], Polina Yonchev [2], Annika Schmid [2], Mara-Noel Weis [2], Lesca-Miriam Holdt [3], Daniel Teupser [3], Simone Kreth [1 2 5 6] Show more

View PDF Download full issue Cite Add to Mendeley Share 10.1016/j.isci.2024.111291 ↗

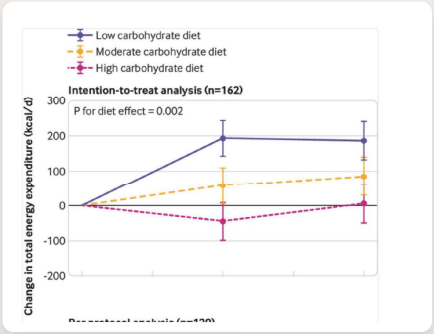
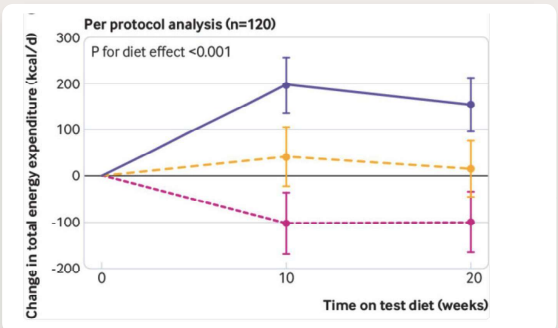


Table5. Body composition of patients with overweight on a three-month KD

	T0	T1	p value
N	25	25	-
Fat fraction [%]	34.76± 1.156	32.12± 1.174	**<0.0001**
Fat mass [kg]	32.50± 1.569	27.85± 1.367	**<0.0001**
Fat free mass [kg]	59.46± 2.151	58.12± 2.163	**<0.0001**
Phase angle [°]	5.453± 0.1214	5.527± 0.1317	**0.0369**
Total body water [kg]	39.76± 1.630	39.09± 1.664	0.0873
Predicted muscle mass [kg]	56.48± 2.051	55.22± 2.062	**<0.0001**
Bone mass [kg]	3.042± 0.1060	2.983± 0.1063	**<0.0001**
Visceral fat mass [kg]	13.93± 1.298	11.89± 1.061	**<0.0001**
Visceral fat level	10.13± 0.8771	8.625± 0.7844	**<0.0001**
Extracellular water [kg]	18.96± 0.5518	18.00± 0.5691	**<0.0001**
Intracellular water [kg]	21.60± 1.191	21.29± 1.191	0.4222



Ketosis appears to have a metabolic advantage

Beyond Weight loss and Blood Sugar

- Blood pressure
- TG/HDL
- LDL particle size
- Blood Pressure
- Inflammatory markers

RESULTS

Using intention-to-treat analyses, compared with the DASH diet, the VLC diet led to greater improvement in estimated mean systolic blood pressure (−9.77 mm Hg vs −5.18 mm Hg; P = .046), greater improvement in glycated hemoglobin (−0.35% vs −0.14%; P = .034), and greater improvement in weight (−19.14 lb vs −10.34 lb; P = .0003). The addition of extra support did not have a statistically significant effect on outcomes.

ANNALS OF FAMILY MEDICINE

Ann Fam Med. 2023 May-Jun;21(3):256–263. doi: 10.1370/afm.2968

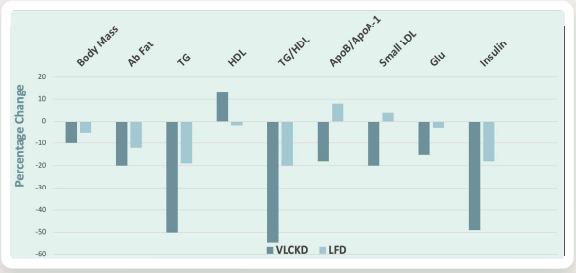
Comparing Very Low-Carbohydrate vs DASH Diets for Overweight or Obese Adults With Hypertension and Prediabetes or Type 2 Diabetes: A Randomized Trial

Laura R Saslow [1,✉], Lenette M Jones [1], Ananda Sen [2,3], Julia A Wolfson [4,5], Heidi L Diez [6,7], Alison O'Brien [1], Cindy W Leung [8], Hovig Bayandorian [1], Jennifer Daubenmier [9], Amanda L Missel [1], Caroline Richardson [7]

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PMCID: PMC10202504 PMID: 37217318

Very Low Carb Lipid and Metabolic Benefits



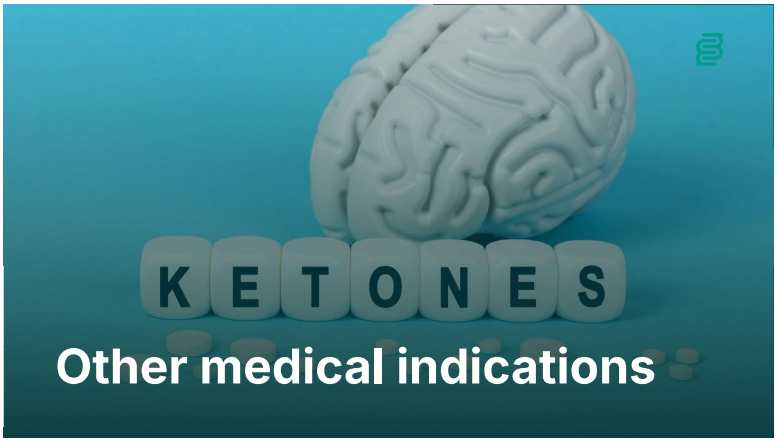
Hite et al, Nutr Clin Pract. 2011

PURPOSE

Adults with a triple multimorbidity (hypertension, prediabetes or type 2 diabetes, and overweight or obesity), are at increased risk of serious health complications, but experts disagree on which dietary patterns and support strategies should be recommended.

METHODS

We randomized 94 adults from southeast Michigan with this triple multimorbidity using a 2 × 2 diet-by-support factorial design, comparing a very low-carbohydrate (VLC) diet vs a Dietary Approaches to Stop Hypertension (DASH) diet, as well as comparing results with and without multicomponent extra support (mindful eating, positive emotion regulation, social support, and cooking).



Other medical indications

Keto Precautions

Absolute contraindications are rare
CPT deficiency, Porphyria, Pyruvate Caroxylase deficiency

Keto Precautions

Absolute contraindications are rare

Precautions are more common

DKA risk

"Keto flu"
Hydration and electrolytes

Keto Precautions

Absolute contraindications are rare

Precautions are more common
Hypoglycemia with insulin, sulfonylurea, etc / Hypotension with BP meds

Keto Precautions

Absolute contraindications are rare

Precautions are more common

DKA risk

"Keto flu"

Lean Mass Hyper Responders (LMHR)

Keto Precautions

Absolute contraindications are rare

Precautions are more common

DKA risk
SGLT2i / Breastfeeding and hypocaloric diet

Ketogenic Diets

Better short term weight loss and glycemic control
Including DM reversal/remission and medication reduction

Better short to medium term metabolic benefits

Metabolic and glycemic benefits may be independent of weight loss

Better reversal of liver steatosis and insulin resistance

Multifactorial mechanisms

Misunderstood and misrepresented risks