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RESEARCH PAPER

Multivitamin restriction increases adiposity and disrupts glucose homeostasis in mice

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Abstract A strong association between obesity and low plasma concentrations of vitamins has been widely reported; however, the causality of this relationship is still not established. Our goal was to evaluate the impact of a multivitamin restriction diet (MRD) on body weight, adiposity and glucose homeostasis in mice. The mice were given a standard diet or a diet containing 50 % of the recommended vitamin intake (MRD) for 12 weeks. At the end of the experiment, total body weight was 6 % higher in MRD animals than in the control group, and the adiposity of the MRD animals more than doubled. The HOMA-IR index of the MRD animals was significantly increased. The adipose tissue of MRD animals had lower expression of mRNA encoding adiponectin and Pnpla2 (47 and 32 %, respectively) and 43 % higher leptin mRNA levels. In the liver, the mRNA levels of Pparα and Pgc1α were reduced (29 and 69 %, respectively) in MRD mice. Finally, the level of β-hydroxybutyrate, a ketonic body reflecting fatty acid oxidation, was decreased by 45 % in MRD mice. Our results suggest that MRD promotes adiposity, possibly by decreasing adipose tissue lipolysis and hepatic β-oxidation. These results could highlight a possible role of vitamin deficiency in the etiology of obesity and associated disorders.

Keywords Vitamins · Obesity · Adiposity · HOMA-IR · Healthy pattern

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Introduction

Obesity is a worldwide health problem that affects more than 10 % of the world's adult population. The World Health Organization (WHO) has identified the increased intake of energy-dense foods that are rich in fat, salt and sugars but poor in vitamins, minerals and other micronutrients, together with decreased physical activity, as major causes of obesity and overweight (WHO 2012).

Indeed, obesity is frequently associated with vitamin deficiency (Garcia et al. 2009). In particular, vitamin D together with B group vitamins has been reported to be deficient in obesity, particularly in morbidly obese individuals. One study highlighted the deficiency of vitamin D and B group vitamins in obesity (Kaidar-Person et al. 2008), whereas another study reported that levels of vitamin B6, vitamin C, 25-hydroxy-vitamin D and lipid-corrected vitamin E were significantly lower in obese

individuals compared with a control population (Aasheim et al. 2008). However, the causality between low vitamin status and obesity remains particularly difficult to establish, especially in humans.

In animal models, several experiments have been performed on pregnant female rats to identify the possible impact of maternal vitamin supplementation or deficiency on offspring phenotype. These experiments suggest that the vitamin content of the diet influences adiposity and body fat content. In fact, multivitamin supplementation (tenfold increase) in rats during pregnancy results in increased food intake and obesity (Szeto et al. 2008, 2009). Interestingly, an increase of body fat content has also been observed in the offspring of female rats receiving a 50 % restricted vitamin diet (Venu et al. 2004). Similarly, a folate and vitamin B12 deficiency in female-weaning rats have been shown to result in increased adiposity in offspring (Kumar et al. 2013).

However, the impact of multivitamin deficiency on the adiposity of adults has never been explored. In the present study, we evaluated adiposity and other parameters, such as glycemia and insulinemia, in mice fed a control diet or multivitamin-restricted diet (MRD) containing 50 % of the required amounts of vitamins. Gene expression analysis was performed to evaluate whether the fat mass gain observed in MRD-fed mice could result, at least in part, from the reduction of adipose lipolysis and hepatic lipid oxidation.

Materials and methods

Animal experiments

The protocol was approved by the local ethics committee. Six-week-old male C57BL/6 J Rj mice were obtained from Janvier (Le Genest Saint Isle, France) and fed ad libitum with a control diet or a diet containing 50 % of the recommended quantity of vitamins (Tables 1, 3), TD06416 and TD10959, respectively, from Harlan (Indianapolis, IN, USA), with full access to drinking water. The animals were maintained in a room at 22 °C on a 12-hour light:12-hour dark cycle with a humidity level of 50 %. In both groups, minerals were supplied as recommended (Table 2). Mice (10 per group) were assigned to one of the two experimental groups depending on their diet, i.e., control or multivitamin restricted, for 10 weeks. Weight gain was measured every week, and energy intake was calculated per cage from the amount of food consumed by the animals and its caloric equivalence. At the end of treatment period, mice were fasted overnight and blood was collected by cardiac venipuncture under anesthesia. Animals were then killed by cervical dislocation. Immediately after dissection, epididymal, peri-renal and inguinal adipose depots were weighed. Liver samples were also collected. Samples were snap-frozen in liquid nitrogen and stored at −80 °C until use.

Table 1 Formula of diets

	Control diet TD06416 (g/kg)	Multivitamin-restricted diet TD10959 (g/kg)
Casein	210	210
L-Cysteine	3	3
Corn starch	280	287.5
Maltodextrin	50	50
Lard	20	20
Soybean oil	20	20
Cellulose	37.15	37.15
Sucrose	325	325
Mineral mix, AIN-93G-MX[a]	35	35
Calcium phosphate, dibasic	2	2
Vitamin mix, AIN-93-VX[b]	15	7.5
Choline bitartrate	2.75	2.75
Estimated energy amount (Kcal/g)	3.7	3.728

[a] Precise composition of mineral mix given in Table 2

[b] Precise composition of vitamin mix given in Table 3

Table 2 Quantity of mineral elements contained in diets

	Control diet TD06416 (mg/kg)	Multivitamin-restricted diet TD10959 (mg/kg)
Calcium	5,000	5,000
Phosphorus	1,561	1,561
Potassium	3,600	3,600
Sulfur	300	300
Sodium	1,019	1,019
Chloride	1,571	1,571
Magnesium	507	507
Iron	35	35
Zinc	30	30
Manganese	10	10
Copper	6	6
Iodine	0.2	0.2
Molybdenum	0.15	0.15
Selenium	0.15	0.15
Silicon	5	5
Chromium	1	1
Fluoride	1	1
Nickel	0.5	0.5
Boron	0.5	0.5
Lithium	0.1	0.1
Vanadium	0.1	0.1

Table 3 Quantity of vitamins contained in diets

	Control diet TD.06416 (U/kg)	Multivitamin-restricted diet TD10959 (U/kg)
Nicotinic acid (mg)	45	22.5
Pantothenate (mg)	22.5	11.25
Pyridoxine (mg)	9	4.5
Thiamin (mg)	7.5	3.75
Riboflavin (mg)	9	4.5
Folic acid (mg)	3	1.5
Vitamin K (μg)	1,125	562.5
D-Biotin (μg)	300	150
Vitamin B-12 (μg)	37.5	18.75
Vitamin A (IU)	6,000	3,000
Vitamin D3 (IU)	1,500	750
Vitamin E (IU)	112.5	56.25

RNA isolation and qPCR

Total RNA was extracted from the tissues (epididymal adipose tissue and liver) using TRIzol reagent according to the manufacturer's instructions (Life Technologies, Saint Aubin, France). RNA purity was evaluated by measuring the absorbance at 260/280 and 260/230 nm ratios using spectrometry. Real-time quantitative PCR analyses were performed using the Mx3005P Real-Time PCR System (Stratagene, La Jolla, CA). For each condition, expression was quantified in duplicate, and 18S rRNA was used as an endogenous control in the comparative cycle threshold (C_T) method. Data were expressed as a relative expression ratio as previously described (Landrier et al. 2008). The primers used in this study are listed in Supplemental Table 1 (Table S1).

Analysis of plasma samples

The glucose concentration in the plasma was evaluated using glucose RTU (bioMerieux, Craponne, France). The insulin concentration in the plasma was quantified using an ELISA kit (Mercodia, Uppsala, Sweden). The β-hydroxybutyrate concentration was measured using a colorimetric test according to the manufacturer's procedure (BEN srl, Milano, Italy). The plasma 25-hydroxy-vitamin D concentration was measured using an ELISA kit (Promokine, Promocell, Heidelberg, Germany). Levels of vitamin E and retinol were quantified by HPLC as previously described (Landrier et al. 2008).

Table 4 Plasma levels of vitamins

	Standard diet mice	Multivitamin-restricted diet mice
Retinol (μmol/l)	0.85 ± 0.3	0.98 ± 0.21
Vitamin E (μmol/l)	3.11 ± 0.77	2.58 ± 0.24
25-OH-VD (nmol/l)	23 ± 3.99	22 ± 3.79

Statistical analysis

Data are expressed as the means ± SEM. Significant differences were determined by unpaired Student's *t* test using Statview software (SAS Institute, Cary, NC). $p < 0.05$ was considered to be statistically significant.

Results

A multivitamin restriction diet (MRD) increased body weight and adiposity

The effect of a MRD containing 50 % of the amount of required vitamins compared with a normal vitamin diet was evaluated in wild-type C57BL/6 J male mice. No differences in plasma levels of retinol, vitamin E or 25-hydroxy-vitamin D were observed between the two groups of animals (Table 4). However, after 12 weeks of the regimen (Fig. 1a), we observed that MRD increased the body weight (6 %) of mice compared with mice receiving the normal vitamin diet (Fig. 1b). This increase of body weight was associated with an increase of fat mass in MRD-fed mice. The masses of all fat pads measured (epididymal, peri-renal and inguinal; Fig. 1c) in MRD mice were twofold higher than those in mice receiving the normal diet. The increase in fat pad mass was maintained after adjustment for body weight (Fig. 1d). Consequently, the calculated adiposity index (ratio sum of fat pads/total mass of mice) was also twofold higher in MRD mice than in mice receiving the normal diet (Fig. 1e). Note that food intake (Fig. 1f) and energy intake (Fig. 1g) were comparable between the two experimental groups, suggesting that the alteration of body weight and adiposity did not result from differences in food intake.

MRD modified AdipoQ and Lep expression in adipose tissue

Because alterations of adipose tissue mass are associated with numerous gene expression modifications, notably the

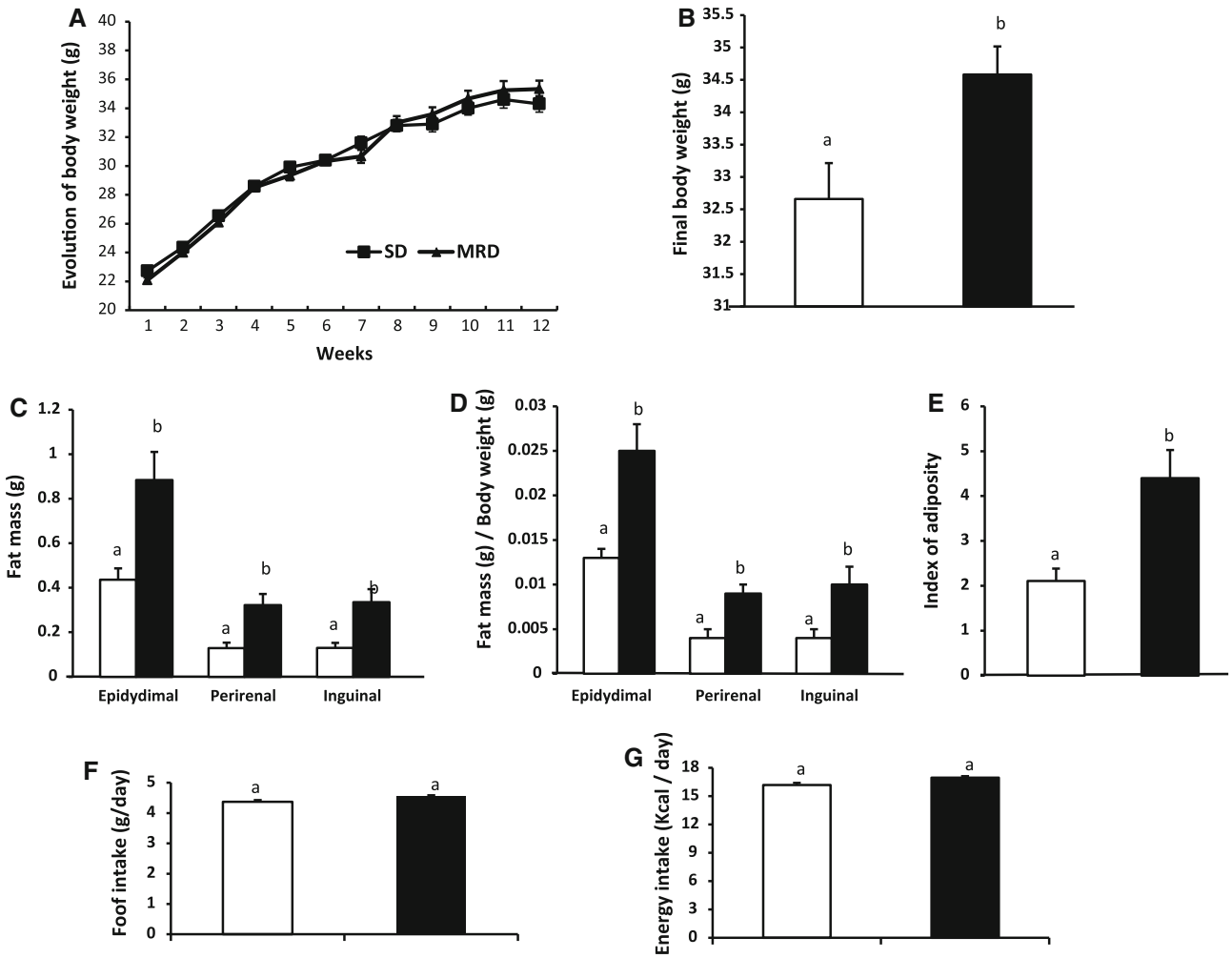

Fig. 1 Multivitamin restriction increases body weight and adiposity. **a** Body weight evolution was followed during the 12 weeks of treatment. **b** Before killing, animal weight was established. **c** At the time of killing, after 12 weeks of treatment, adipose tissues (epididymal, subcutaneous and peri-renal) were weighed for each animal ($n = 10$). **d** The fat mass is reported relative to the total body weight of the animal. **e** An adiposity index was calculated by calculating the ratio between total fat mass and body weight for the animal. **f** Mean food intake was determined together with energy intake. **g** *White bars* correspond to mice submitted to the standard diet (SD), and *black bars* correspond to mice submitted to the multivitamin-restricted diet. Values are presented as the mean ± SEM. *Bars* not sharing the *same letter* are significantly different, $p < 0.05$

expression of adiponectin and leptin (Carbone et al. 2012), the mRNA levels of these two adipokines were quantified in epididymal adipose tissues by qPCR. In agreement with the observed alterations of epididymal fat pad mass, mRNA levels of AdipoQ were decreased by 47 % in MRD mice compared with mice receiving the normal diet, whereas mRNA levels of Lep were increased by 43 % (Fig. 2).

MRD increased fasted insulinemia and HOMA-IR

Fasting glycemia and insulinemia were quantified and were not significantly different between the two experimental conditions, although insulinemia tended to increase ($p = 0.059$) in the MRD group. However, the HOMA-IR index was significantly increased by 43 % in MRD mice compared with mice receiving the normal diet (Fig. 3).

MRD altered levels of plasma markers of fatty acid oxidation, white adipose tissue and hepatic gene expression

Because the food intake of the mice was not affected by the MRD, we hypothesized that the energy metabolism was modified. Triglyceride lipolysis and fatty acid β-oxidation were explored through the expression of patatin-like phospholipase domain containing 2 (Pnpla2), the transcription factor Pparα and a cofactor governing fatty acid

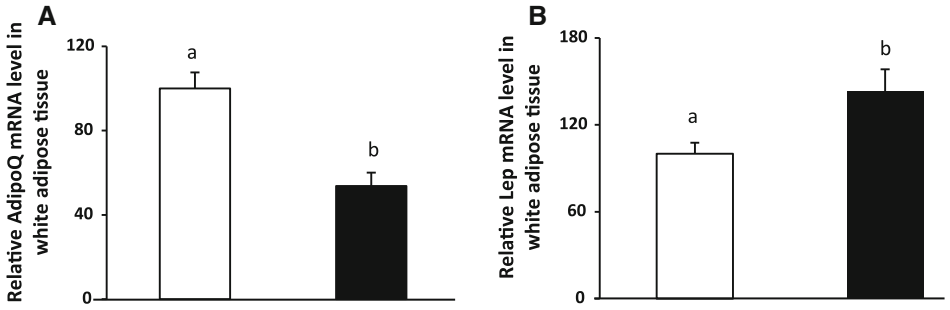

Fig. 2 Multivitamin restriction modifies AdipoQ and Lep expression in adipose tissue. **a**, **b** Gene expression in white adipose tissue is expressed relative to 18S ribosomal RNA levels in mice submitted to a standard diet (*white bars*) and multivitamin-restricted diet (*black bars*) for 12 weeks ($n = 10$). Values are presented as the mean ± SEM. *Bars* not sharing the *same letter* are significantly different, $p < 0.05$

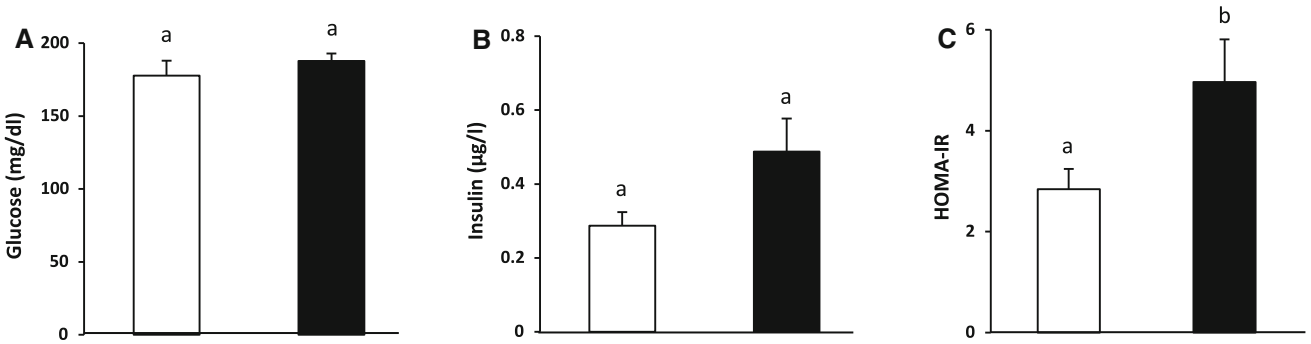

Fig. 3 Multivitamin restriction increases fasted insulinemia and HOMA-IR. **a**, **b** Insulin and glucose levels were measured after overnight fasting in the plasma of mice that received the standard diet (*white bars*) or multivitamin-restricted diet (*black bars*) for 12 weeks ($n = 10$). **c** The HOMA-IR index was calculated based on glycemia and insulinemia. Values are presented as the mean ± SEM. *Bars* not sharing the same letter are significantly different, $p < 0.05$

oxidation in liver, Ppargc1α. The mRNA level of Pnpla2 was decreased by approximately 40 % under MRD. In addition, the mRNA levels of Ppara and Ppargc1α were strongly decreased in MRD, by approximately 29 and 69 %, respectively. To monitor fatty acid oxidation, the plasma concentration of the ketonic body β-hydroxybutyrate was assayed because in the fasted state, this ketonic body is produced by β-oxidation of fatty acids. A reduction of 40 % in the β-hydroxybutyrate level was observed in MRD mice, suggesting lower oxidation of fatty acids in MRD mice compared to those receiving the normal diet (Fig. 4).

Discussion

The present study showed for the first time that a multivitamin restriction diet (MRD) administered to adult mice increases their body weight and fat mass and disrupts glucose homeostasis. Because the MRD did not alter food intake, our results highlight that lipolysis in adipose tissue and hepatic fatty oxidation is impacted by multivitamin restriction, suggesting that modifications of lipid metabolism are associated with the observed phenotype, although we cannot exclude modifications of activity or thermogenesis, which were not measured in the present study.

We report here that a 50 % restriction of vitamin supply is sufficient to modify the body weight and fat content of mice compared with a normal diet containing quantities of vitamins based on recommendations of the National Research Council Handbook (Subcommittee on Laboratory Animal Nutrition 1995). Nevertheless, it is necessary to consider that these recommendations are based on limited evidence, and it is currently considered that vitamins are present in large excess in rodent diets. However, our results agree with previous findings that vitamin inadequacy may influence several physiological processes, including immune response or energy homeostasis.

The goal of our study was to evaluate the impact of a global vitamin restriction, and not to evaluate the specific effect of each vitamin, because many studies have already reported the impact of isolated vitamin restriction/

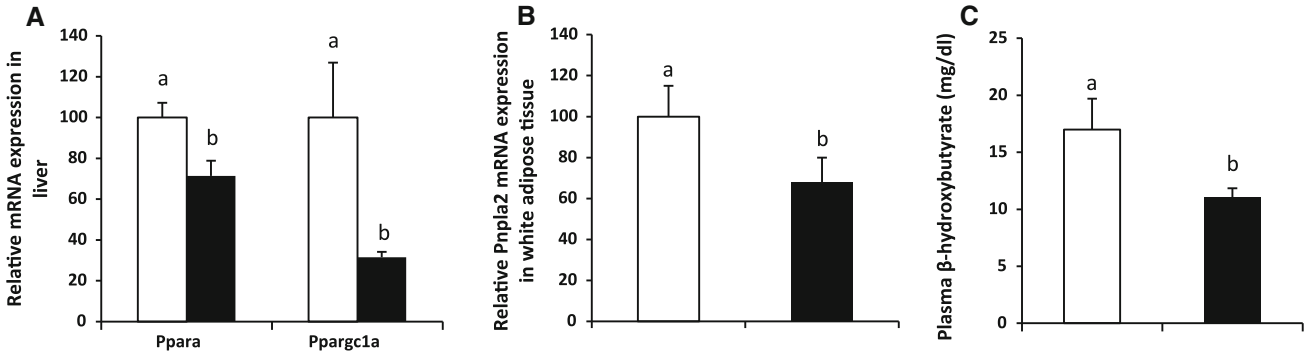

Fig. 4 Multivitamin restriction decreases gene expression in the liver and white adipose tissue and β-hydroxybutyrate levels in plasma. Gene expression relative to 18S ribosomal RNA levels in the liver (**a**) and in white adipose tissue (**b**) of mice ($n = 10$) submitted to the standard diet (*white bars*) and multivitamin-restricted diet (*black bars*) for 12 weeks. **c** β-Hydroxybutyrate concentration in plasma of mice ($n = 10$) submitted to the standard diet (*white bars*) and multivitamin-restricted diet (*black bars*) for 12 weeks. Values are presented as the mean ± SEM. *Bars* not sharing the same letter are significantly different, $p < 0.05$

supplementation on body weight management and adiposity. Indeed, vitamin A and its metabolites, i.e., retinoids (including *all-trans* retinoic acid and retinaldehyde) have been shown to reduce adiposity and body weight in several animal models (Bonet et al. 2000, 2003; Berry and Noy 2009; Ziouzenkova et al. 2007; Landrier et al. 2012; Tourniaire et al. 2009), and a low vitamin A status has been associated with an increase in white adipose tissue content (Bonet et al. 2000; Ribot et al. 2001). In addition, the regulation of RBP4 by vitamin A metabolites (Mercader et al. 2008) may also participate in the observed effect on insulin sensitivity. Low vitamin D intake could influence body weight and adiposity, and although the causality has not been proven, numerous epidemiological (cross-sectional and prospective) studies have shown a negative association between low levels of 25-hydroxy-vitamin D, the circulating form of vitamin D and obesity and associated pathologies (Garcia et al. 2009; Soares et al. 2011). Obese individuals have also been shown to have a lower level of the antioxidant vitamins C and E (Aasheim et al. 2008). Although the impact of vitamin E supplementation or deficiency on obesity in an animal model has never been reported, vitamin C supplementation has been shown to reduce the body weight of rats fed a cafeteria diet (Campion et al. 2006), suggesting that an adequate vitamin C level may participate in body weight management. Vitamin E has been shown to impact adipocyte biology, leading to modulation of the secretion of adipokines (Landrier et al. 2009, 2012). Finally, the vitamin B group has also been negatively associated with overweight or obesity (Garcia et al. 2009; Aasheim et al. 2008). Within this vitamin group, few members are suspected to display a role in body weight management. However, thiamine (B1 vitamin) has been shown to prevent obesity and associated metabolic disorders in obese OLETF rats (Tanaka et al. 2010). Pantothenic acid (B5 vitamin) may also influence body weight gain and lipid metabolism in obese mice (Naruta and Buko 2001), and nicotinic acid (B3 vitamin) increased adiponectin expression (Wanders et al. 2013), suggesting a specific effect of this vitamin on adipose tissue biology.

The present study, which highlights the impact of a global vitamin restriction on body weight and adiposity, paves the way for additional to determine a putative additive or synergistic effect of multivitamin restriction on body weight gain and increased adiposity compared with isolated vitamin restriction. However, it is necessary to consider that no modification of the plasma levels of the vitamins tested (retinol, vitamin E and 25-hydroxy-vitamin D) was observed. It should be noted that not all vitamins were quantified in the plasma; additionally, it would have been interesting to quantify vitamin levels in adipose tissue, which would have been even more relevant. This point represents a limitation of the present work, which will require further investigation.

Our study points to some molecular mechanisms related to lipid metabolism. First, Pnpla2 mRNA levels were reduced in the epididymal fat pads of MRD mice. Pnpla2 was the first lipolysis enzyme discovered that provides substrates for hormone-sensitive lipase (Zimmermann et al. 2004, 1140), and its role in lipolysis has been notably demonstrated in vivo. Indeed, Pnpla2$^{-/-}$ mice present weight gain and increased adipose mass because of triglyceride accumulation (Haemmerle et al. 2006). Conversely, transgenic mice overexpressing Pnpla2 in adipose tissue display elevated lipolysis and increased fatty acid oxidation (Ahmadian et al. 2009). Together, these data suggest that decreased Pnpla2 expression could contribute to increased fat deposition, as observed in our study, through a reduction of lipolysis. In the liver, we observed that Ppargc1a and Ppara gene expression were significantly decreased in MRD mice. It is noteworthy that these genes encode key transcription factor regulators of hepatic FA

oxidation because β-oxidation is impaired in both Ppargc1a$^{-/-}$ and Ppara$^{-/-}$ mice (Wu et al. 1999; Lee et al. 1995). Thus, the reduced fatty acid flux consequent to lipolysis decrease may reduce hepatic fatty acid oxidation, as revealed by down-regulation of Ppara and Ppargc1a. Additionally, we quantified β-hydroxybutyrate, a ketone body, in the plasma of mice. In the fasted state, ketone bodies arise from the β-oxidation of fatty acids that are primarily liberated from the lipolysis of the stored triglycerides in adipose tissue (Vice et al. 2005). Thus, the observed decrease of β-hydroxybutyrate observed in MRD mice is fully consistent with the hypothesis that restricted vitamin intake decreases adipose lipolysis and decreases β-oxidation in the liver. Nevertheless, the establishment of a causal relationship between these events and the identification of molecular mechanisms governing these gene modulations will require further investigation.

From a clinical point of view, these data strongly reinforce the putative role of vitamin inadequacy in the etiology of obesity, as previously suggested by others (Astrup and Bugel 2010). Our data are consistent with a cross-sectional study showing that men consuming multivitamins and dietary supplements had lower body weight, fat mass and BMI (Major et al. 2008). Interestingly, a 10-year longitudinal study showed that long-term use of multivitamins is associated with lower levels of weight gain in overweight and obese subjects (Nachtigal et al. 2005). Finally, our results are also partly in agreement with a recent clinical trial that determined the effect of a multivitamin and mineral supplementation in obese Chinese women (Li et al. 2010). In that study, a lower body weight, lower fat mass and improvement of several parameters, including lipemia, were observed at the end of the supplementation. However, such supplementation involves both vitamins and minerals, whereas minerals were not studied in our experiments; thus, we cannot rule out the specific role of minerals in the reduction of body and fat mass.

To conclude, our study in mice suggests a role for vitamin insufficiency in obesity, although extensive further work is still required. Vitamin deficiency based on consumption of inexpensive but vitamin-poor foods may play a role in body weight and adiposity management (Kimmons et al. 2006). Our study contributes to the recommendation of a healthy diet composed of diverse food products with high vitamin density, such fruit and vegetables, whole-grain cereals and fish products.

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Conflict of interest N.B.A., J.M., F.T., J.A., M.J.A., P.D. and J.F.L. declare that they have no conflict of interest.

Ethical standard All institutional and national guidelines for the care and use of laboratory animals were followed.

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