J Appl Physiol 95: 2180–2182, 2003;
10.1152/japplphysiol.00563.2003.

The following is the abstract of the article discussed in the subsequent letter:

Nissen, Steven L., and Rick L. Sharp. Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. *J Appl Physiol* 94: 651–659, 2003. The purpose of this study was to quantify which dietary supplements augment lean mass and strength gains during resistance training. Peer-reviewed studies between the years 1967 and 2001 were included in the analysis if they met a predetermined set of experimental criteria, among which were at least 3-wk duration and resistance-training 2 or more times a week. Lean mass and strength were normalized for meta-analysis by conversion to percent change per week and by calculating the effect size for each variable. Of the 250 supplements examined, only 6 had more than 2 studies that met the criteria for inclusion in the meta-analysis. Creatine and β-hydroxy-β-methylbutyrate (HMB) were found to significantly increase net lean mass gains of 0.36 and 0.28%/wk and strength gains of 1.09 and 1.40%/wk ($P < 0.05$), respectively. Chromium, dehydroepiandrosterone, androstenedione, and protein did not significantly affect lean gain or strength. In conclusion, two supplements, creatine and HMB, have data supporting their use to augment lean mass and strength gains with resistance training.

HMB meta-analysis and the clustering of data sources

To the Editor: In a recent meta-analysis of the clinical efficacy of dietary supplements to increase lean body mass and strength with resistance training (3), 250 candidate supplements were screened. Six had more than two studies that met the criteria for inclusion, and ultimately two came out as providing significant benefit: creatine and β-hydroxy-β-methylbutyrate (HMB). The publication of these results is likely to have a significant impact on the purchasing decisions of those resistance-training enthusiasts who seek body enhancement through the use of supplements.

Nissen and Sharp (3) conducted and thoroughly described an excellent methodology for the analysis. Only randomized, placebo-controlled clinical studies published in peer-reviewed journals were selected. Inclusion criteria based on all quality and homogeneity requirements were applied with great care. However, one aspect was not discussed: the interdependence of the scrutinized studies listed in their Table 1 (3). We examined the studies bearing on creatine and HMB with regard to relations between all authors and between institutions where the investigations were done (Fig. 1). We found that the nine studies on HMB clustered around three unrelated groups of researchers. The 18 studies on creatine clustered into 14 unrelated groups of researchers. Demonstrations of efficacy produced by only a small number of separate sources are intuitively less persuasive than those from a large number of independent laboratories. Among reasons for this, we believe that investigations led by connected authors or institutions are likely to share similar approaches to a given question and use a smaller variety of methods than truly independent ones.

We respectively add a few comments. *1*) It would have been useful if the authors had presented in their summary table the calculated effect size (2) of each of the included studies, thus allowing the reader to replicate the pooled effect. *2*) On the basis of funnel-plot analysis, the authors deemed the likelihood of a publication bias weak (small positive trials are more likely to be published than negative ones). Funnel plots, which estimate the effect size obtained in studies relative to their sample size, spot biases because results of smaller studies are more scattered than those of larger studies (1). However, medium- and large-sized trials seem necessary to conduct funnel plot analysis. It is unlikely that with only small-sized trials (6 to 21 subjects in the HMB studies) an asymmetry should have appeared in funnel plots (data were not shown). Therefore, we believe that a statement mitigating the likelihood of publication bias is not justified. *3*) Retrospective selectivity is a possible source of error (4). The decision to perform and publish a meta-analysis is inspired by prior knowledge, which would have motivated the authors to invest the necessary effort to conduct the meta-analysis. The danger is that "the

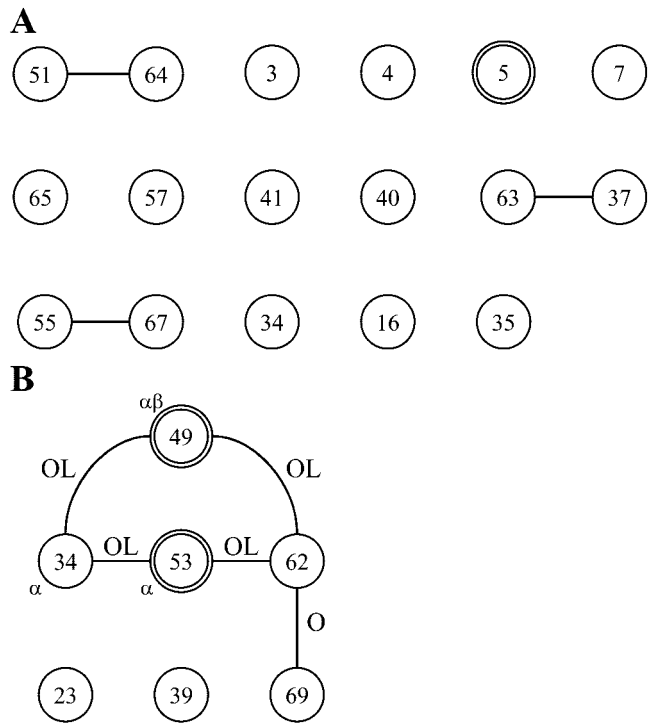

Fig. 1. Collaborations between authors of the efficacy studies selected for meta-analysis, and institutions supporting them. *A*: creatine, 14 clusters. *B*: β-hydroxy-β-methylbutyrate (HMB), 3 clusters. *Circled* numbers identify published papers as referenced in Ref. 3. *Doubly circled* references are those including two separate investigations in the same paper. *Lines* indicate that some authors or institutions are common to the connected papers. Circles without a line appear to be fully independent studies. Authors of meta-analyses (3) are identified with α and β. O, institution that owns the patents related to HMB. L, corporation that is the licensee of the HMB patents.

Table 1. *Addition to original Table 1 (see Ref. 1) giving net effect sizes for all studies meeting the inclusion criteria*

Author	Year	Journal	Net Effect Size	
			Lean gain	Strength gain
		Creatine		
Arciero et al. (3)	2001	*Metabolism*	0.23	0.56
Bemben et al. (4)	2001	*Med Sci Sports Exerc*	0.50	0.27
Bermon et al. (5)	1998	*Acta Phys Scand*	NA	0.21
Bermon et al. (5)	1998	*Acta Phys Scand*	NA	0.10
Brenner et al. (7)	2000	*J Strength Cond Res*	0.11	0.25
Chrusch et al. (16)	2001	*Med Sci Sports Exerc*	0.46	0.51
Jowko et al. (34)	2001	*Nutrition*	0.16	0.45
Kelly et al. (35)	1998	*J Strength Cond Res*	0.17	0.25
Kirksey et al. (37)	1999	*J Strength Cond Res*	0.12	NA
Kreider et al. (40)	1998	*Med Sci Sports Exerc*	0.09	NA
Larson-Meyer et al. (41)	2000	*J Strength Cond Res*	0.07	0.50
Noonan et al (51)	1998	*J Strength Cond Res*	0.15	0.54
Pearson et al. (55)	1999	*J Strength Cond Res*	NA	0.22
Peeters et al. (57)	1999	*J Strength Cond Res*	0.19	0.17
Stone et al. (63)	1999	*Int J Sports Nutr*	0.59	0.29
Stout et al. (64)	1999	*Nutr Res*	0.48	0.66
Vandenberghe et al. (65)	1997	*J Appl Physiol*	0.29	0.39
Volek et al. (67)	1999	*Med Sci Sports Exerc*	0.23	0.31
	Average		0.26	0.36
		HMB		
Gallagher et al. (23)	2000	*Med Sci Sports Exerc*	0.22	0.16
Jowko et al. (34)	2001	*Nutrition*	0.20	0.46
Kreider et al. (39)	1999	*Int J Sports Med*	0.05	0.06
Nissen et al. (short) (49)	1996	*J Appl Physiol*	0.14	0.09
Nissen et al. (long) (49)	1996	*J Appl Physiol*	0.15	0.32
Panton et al. (men) (53)	2000	*Nutrition*	0.08	0.36
Panton et al. (wom) (53)	2000	*Nutrition*	0.06	0.22
Slater et al. (62)	2001	*Int J of Sport Nutr*	0.43	−0.05
Vukovich et al. (69)	2001	*J Nutr*	0.03	0.11
	Average		0.15	0.19
		Chromium		
Boyd et al. (6)	1998	*J Nutr Biochem*	NA	−0.10
Campbell et al. (14)	1999	*J Appl Physiol*	−0.07	−0.16
Clancy et al. (17)	1994	*Int J Sports Nutr*	−0.28	0.16
Hallmark et al. (29)	1996	*Med Sci Sports Exerc*	0.07	−0.33
Hasten et al. (30)	1992	*Int J Sports Nutr*	NA	−0.16
Hasten et al. (30)	1992	*Int J Sports Nutr*	NA	0.38
Joseph et al. (33)	1999	*Metabolism*	−0.12	NA
Joseph et al. (33)	1999	*Metabolism*	0.15	NA
Livolsi et al. (43)	2001	*J Strength Cond Res*	0.14	0.88
Lukaski et al. (44)	1996	*Am J Clin Nutr*	0.07	0.11
Volpe et al. (68)	2001	*J Am Coll Nutr*	0.26	0.17
Walker et al. (70)	1998	*Med Sci Sports Exerc*	−0.03	−0.12
	Average		0.02	0.08
		Androstenedione		
Broeder et al. (9)	2000	*Arch Intern Med*	0.13	−0.11
King et al. (36)	1999	*JAMA*	−0.01	−0.08
Wallace et al. (71)	1999	*Med Sci Sports Exerc*	0.03	NA
	Average		0.05	−0.10
		Dehydroepiandrosterone		
Brown et al. (10)	1999	*J Appl Physiol*	0.13	−0.03
Wallace et al. (71)	1999	*Med Sci Sports Exerc*	0.01	NA
	Average		0.07	−0.03
		Protein		
Burke et al. (11)	2001	*Int J Sport Nutr*	0.19	0.00
Campbell et al. (13)	1995	*Am J Physiol*	0.11	NA
Lemon et al. (42)	1992	*J Appl Physiol*	0.01	−0.14
Nissen et al. (short) (49)	1996	*J Appl Physiol*	−0.03	0.10
	Average		0.07	−0.01

See Ref. 1 for full reference citations. NA, not available due to insufficient data to calculate effect size (absence of a SE or SD and/or *N* size). HMB, β-hydroxyl-β-methylbutyrate.

observed benefits that trigger the analysis are quite likely to have been exaggerated by chance" (4).

It is our opinion that, until further data are produced by independent sources, claims of efficacy for HMB as an aid during resistance training for the development of lean body mass are not as robust as those for creatine and should be considered with reservation.

REFERENCES

1. **Egger M and Smith GD.** Misleading meta-analysis: lessons from "an effective, safe, simple" intervention that wasn't. *BMJ* 310: 752–754, 1995.
2. **Glass GV.** Integrating findings: the meta-analysis of research. *Rev Res Edu* 5: 351–379, 1977.
3. **Nissen SL and Sharp RL.** Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. *J Appl Physiol* 94: 651–659, 2003. [Corrigenda. *J Appl Physiol* 94: April 2003, following table of contents.]
4. **Yusuf S and Flather M.** Magnesium in acute myocardial infarction. *BMJ* 310: 751–752, 1995.

Jacques Décombaz
Alexandre Bury
Corinne Hager
Nestle Research Center
Nestec Ltd.
CH-1000 Lausanne 26, Switzerland
E-mail: jacques.decombaz@rdls.nestle.com

REPLY

To the Editor: In the letter by Décombaz et al., concerns were raised regarding the interdependence of the studies, unforeseen bias, and the usefulness of the calculated effect sizes of each of the included studies.

In general, we agree with the points raised in the letter. In retrospect, the individual effect sizes should have been included in the manuscript, especially since the presentation of individual effect sizes can then be used in the future, as new data in this area become available. Therefore, we have updated the original Table 1 from our study (1) by adding two columns containing the net effect sizes for lean and strength gains (Table 1).

By comparing the effect sizes of the associated and unassociated studies, it is possible to address the question raised by Dr. Décombaz's group related to the interdependence of the studies. For example, the average effect size for HMB lean gain for the associated studies was 0.16, whereas the mean of the two unassociated studies was 0.14. Furthermore, the range of effect sizes within the associated studies was 0.03–0.43, which encompassed both of the effect sizes for the unassociated studies. With all effect sizes for the HMB studies being generally similar and the ranges of the associated studies including the unassociated studies, it seems unlikely that any source of systematic bias explains the difference. The small numerical differences are more likely to result from varying procedures, dosages, measurements, and subject variability.

The presented meta-analysis was not intended to be a definitive statement or an end-all conclusion; on the contrary, it is to provide a foundation for others to build on. Implicit to this statement is the importance of having sufficient data in all manuscripts to calculate effect sizes or, better yet, the inclusion of effect sizes as part of the original manuscript data.

REFERENCES

1. **Nissen SL and Sharp RL.** Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. *J Appl Physiol* 94: 651–659, 2003.

Steven L. Nissen
Department of Animal Science
Iowa State University
Ames, Iowa 50011

Rick L. Sharp
Department of Health and Human Performance
Iowa State University
Ames, Iowa 50011