ΠΑΝΕΠΙΣΤΗΜΙΟ ΚΡΗΤΗΣ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΕΡΓΑΣΤΗΡΙΟ ΚΛΙΝΙΚΗΣ ΧΗΜΕΙΑΣ

OBESITY, CHRONIC LOW GRADE INFLAMMATION and COGNITION IMPAIRMENT

Παχυσαρκία, χρόνια χαμηλού βαθμού φλεγμονή και γνωστικά ελλείμματα

ΕΙΡΗΝΗ Χ. ΣΠΥΡΙΔΑΚΗ

ψυχολόγος

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

ΗΡΑΚΛΕΙΟ 2015

ΕΞΕΤΑΣΤΙΚΗ ΕΠΙΤΡΟΠΗ

ΜΑΡΓΙΩΡΗΣ Ν. ΑΝΔΡΕΑΣ, Καθηγητής Κλινικής Χημείας-Βιοχημείας (επιβλέπων)

ΣΙΜΟΣ ΠΑΝΑΓΙΩΤΗΣ, Καθηγητής Αναπτυξιακής Νευροψυχολογίας (συνεπιβλέπων)

ΔΑΦΕΡΜΟΣ ΒΑΣΙΛΕΙΟΣ, Αναπληρωτής Καθηγητής Κοινωνικής Στατιστικής (συνεπιβλέπων)

ΒΕΝΙΧΑΚΗ ΜΑΡΙΑ, Επίκουρη Καθηγήτρια Κλινικής Χημείας

ΚΑΡΑΔΗΜΑΣ ΕΥΑΓΓΕΛΟΣ, Αναπληρωτής Καθηγητής Ψυχολογίας της Υγείας

ΚΑΣΤΑΝΑΣ ΗΛΙΑΣ, Καθηγητής Εργαστηριακής Ενδοκρινολογίας

ΤΣΑΤΣΑΝΗΣ ΧΡΗΣΤΟΣ, Αναπληρωτής Καθηγητής Κλινικής Χημείας

Η έγκριση της διδακτορικής διατριβής από το Ιατρικό τμήμα της Σχολής Επιστήμων Υγείας δεν σημαίνει και αποδοχή των απόψεων του συγγραφέα. (Ν5343/1932, άρθρο 202).

Η παρούσα έρευνα έχει συγχρηματοδοτηθεί από την Ευρωπαϊκή Ένωση (Ευρωπαϊκό Κοινωνικό Ταμείο - ΕΚΤ) και από εθνικούς πόρους μέσω του Επιχειρησιακού Προγράμματος «Εκπαίδευση και Δια Βίου Μάθηση» του Εθνικού Στρατηγικού Πλαισίου Αναφοράς (ΕΣΠΑ) – Ερευνητικό Χρηματοδοτούμενο Έργο: Ηράκλειτος ΙΙ. Επένδυση στην κοινωνία της γνώσης μέσω του Ευρωπαϊκού Κοινωνικού Ταμείου.

Ευρωπαϊκή Ένωση
Ευρωπαϊκό Κοινωνικό Ταμείο

ΕΠΙΧΕΙΡΗΣΙΑΚΟ ΠΡΟΓΡΑΜΜΑ
ΕΚΠΑΙΔΕΥΣΗ ΚΑΙ ΔΙΑ ΒΙΟΥ ΜΑΘΗΣΗ
επένδυση στην κοινωνία της γνώσης
ΥΠΟΥΡΓΕΙΟ ΠΑΙΔΕΙΑΣ & ΘΡΗΣΚΕΥΜΑΤΩΝ, ΠΟΛΙΤΙΣΜΟΥ & ΑΘΛΗΤΙΣΜΟΥ
ΕΙΔΙΚΗ ΥΠΗΡΕΣΙΑ ΔΙΑΧΕΙΡΙΣΗΣ

ΕΣΠΑ 2007-2013
πρόγραμμα για την ανάπτυξη
ΕΥΡΩΠΑΪΚΟ ΚΟΙΝΩΝΙΚΟ ΤΑΜΕΙΟ

Με τη συγχρηματοδότηση της Ελλάδας και της Ευρωπαϊκής Ένωσης

Στον Χ.Σ.

(1940-2001)

Ευχαριστίες

Θα ήθελα να ευχαριστήσω πολύ τον επιβλέποντα της διατριβής μου, καθηγητή Κλινικής Χημείας-Βιοχημείας *Μαργιωρή Ν. Ανδρέα* για την εμπιστοσύνη του, όχι σε εμένα αλλά γενικά στους ανθρώπους. Σπάνια έχει κανείς την ευκαιρία να γνωρίζει ένα πραγματικό πρόσωπο που να δίνει στη φράση «αξία ανεκτίμητη» το πλήρες νόημα της.

Τον *Άκη Σίμο,* καθηγητή Αναπτυξιακής Νευροψυχολογίας, γιατί 10 λεπτά συζήτησης μαζί του μεταφράζονται σε τουλάχιστον 100 ώρες διαβάσματος, 1000 ώρες ψυχοθεραπείας και το ελάχιστο σε μερικά δισεκατομμύρια πιο «έξυπνους» νευρώνες. Με λίγα λόγια σε ένα πιο χαρούμενο εγκέφαλο.

Τον αναπληρωτή καθηγητή Κοινωνικής Στατιστικής *Δαφέρμο Βασίλειο*, γιατί το ανεξάντλητο πάθος του για τη στατιστική μπορεί να πείσει για την αξία της ακόμα και τον πλέον αλλεργικό στα μαθηματικά.

Τα μέλη της εξεταστικής επιτροπής: τον καθηγητή Εργαστηριακής Ενδοκρινολογίας *Καστανά Ηλία*, τον αναπληρωτή καθηγητή Κλινικής Χημείας *Τσατσάνη Χρήστο*, τον αναπληρωτή καθηγητή Ψυχολογίας της Υγείας *Καραδήμα Ευάγγελο* και φυσικά την επίκουρη καθηγήτρια Κλινικής Χημείας *Βενιχάκη Μαρία* για την προσεκτική ανάγνωση του κειμένου και τις εύστοχες παρατηρήσεις τους. Η συμμετοχή τους στην επταμελή μου είναι όχι απλά τιμή αλλά κυρίως μεγάλη χαρά.

Την γιατρό-ενδοκρινολόγο *Αυγουστινάκη Παυλίνα* (MD, PhD) για την χωρίς δεύτερη σκέψη προσφορά φιλίας, τον ενθουσιασμό και την πεισματική αισιοδοξία που τόσο ανάγκη έχει πολλές φορές η έρευνα.

Την χημικό *Δερμιτζάκη Ρένα* (PhD) για την ανεξάντλητη διάθεση βοήθειας, την υπομονή, την γλυκύτητα, την στωική και φιλοσοφημένη στάση της για τη ζωή και κατ' επέκταση την έρευνα.

Τον καθηγητή Σχολικής Ψυχολογίας *Αχιλλέα Μπάρδο* για την ευγενική παραχώρηση της άδειας χρήσης του βασικού ερευνητικού εργαλείου GAMA.

Τα παιδία του εργαστήριου κλινικής χημείας που απάλυναν το άγχος μου για την εργασία στον πάγκο και με καθοδήγησαν στη σύντομη σχέση μου με τις πιπέτες, τα διαλύματα και πολλές ακόμα παρόμοιες λέξεις μιας γλώσσας άγνωστης. Πολλά ευχαριστώ λοιπόν στη *Ρασούλη Όλγα*, ήδη διδάκτορα του εργαστηρίου μας, τις συνυποψήφιες διδάκτορες *Καραγιάννη Έφη*, *Ιερωνυμάκη Ρίτσα, Πλατή Ιωάννα* αλλά και όλα τα παιδία που κατά καιρούς συνυπήρξαμε στην πτέρυγα 3Γ.

Τους μικροβιολόγους *Γιώργο, Γιάννα, Αφροδίτη, Ζωή, Κωνσταντίνα* για την πολύτιμη βοήθειά τους στη συλλογή των δειγμάτων αίματος όπως και όλους φυσικά τους συμμετέχοντες στην έρευνα. Αν έλειπε η δική τους εθελοντική προσφορά σε χρόνο και καλή διάθεση τίποτα από όλα αυτά δεν θα ήταν εφικτό.

Τους συναδέλφους ψυχολόγους στο εργαστήριο Νευροψυχολογίας και ιδιαιτέρως τον *Παπαστεφανάκη Μάνο*, για την αμέριστη πρακτική και ηθική συμπαράσταση.

Τον καθηγητή Κλινικής και Πειραματικής Ψυχολογίας του Πάντειου Πανεπιστημίου *Μέλλον Ρόμπερτ*, γιατί «η πρόσβαση στα γλυκούτσικα της ζωής» εξαρτάται χωρίς καμία αμφιβολία από την παρουσία ανθρώπων και δασκάλων σαν και εκείνον.

Τους παλιούς φίλους για τη στήριξη και τους νέους για την υπομονή.

Την μητέρα και τον αδερφό μου, για όλα φυσικά.

Αυτούς που λείπουν για το ότι υπήρξαν πάντα εκεί.

Φεβρουάριος 2015

Περίληψη διατριβής

Η παχυσαρκία οδηγεί σε χρόνιες μεταβολικές διαταραχές όπως αντίσταση στην ινσουλίνη, διαβήτη, αρτηριοσκλήρυνση, υπέρταση καθώς και σύνδρομο αποφρακτικής υπνικής άπνοιας, οι οποίες με τη σειρά τους έχουν συνδεθεί με γνωστικές διαταραχές. Ωστόσο, συνεχώς αυξανόμενα δεδομένα δείχνουν ότι η χαμηλή επίδοση των παχύσαρκων ατόμων σε πλειάδα νευροψυχολογικών τεστ είναι ανιχνεύσιμη ακόμα και ανεξάρτητα από την παρουσία των παραπάνω παθολογικών καταστάσεων. Γνωστικά ελλείμματα μη συνδεόμενα με τις κλινικές συνέπειες της παχυσαρκίας έχουν εντοπιστεί τόσο στη μνήμη όσο και στις επιτελικές λειτουργίες. Οι τελευταίες, συνδέονται με την ρέουσα νοημοσύνη και αποτελούν ανώτερες, σύνθετες γνωστικές λειτουργίες που συμβάλλουν στο συντονισμό και απαρτίωση άλλων απλούστερων νοητικών διεργασιών (π.χ. μνήμη, γλώσσα, κινητικές λειτουργίες) για την ολοκλήρωση στοχοπροσανατολισμένων σκέψεων και δράσεων.

Η χρόνια χαμηλού βαθμού φλεγμονή (chronic low grade inflammation, CLGI) αποτελεί μια από τις πρώτες επιπτώσεις της παχυσαρκίας και συνεισφέρει σημαντικά στην ανάπτυξη όλων των άλλων παθοφυσιολογικών συνεπειών της. Δεδομένα από πολλαπλές πηγές την εμπλέκουν στην παθολογική μείωση γνωστικών ικανοτήτων όπως είναι η άνοια ή η ήπια γνωστική διαταραχή σε ηλικιωμένα άτομα, ακόμα και ανεξάρτητα από την παράλληλη ανάπτυξη μεταβολικών ή καρδιαγγειακών προβλημάτων. Ακόμα πιο σημαντικό είναι το γεγονός ότι υπάρχουν αυξημένες ενδείξεις που συνδέουν την CLGI με χαμηλές γνωστικές επιδόσεις σε υγιή άτομα μέσης ή και νεαρής ηλικίας.

Μια υπόθεση για τη σχέση της παχυσαρκίας με τις γνωστικές ικανότητες είναι ότι η πρώτη μπορεί να οδηγήσει είτε άμεσα είτε έμμεσα, σε διαταραχές στην λειτουργία του εγκεφάλου, οι οποίες εκδηλώνονται με μειωμένη γνωστική επίδοση. Εναλλακτικά, και με

δεδομένο ότι οι επιτελικές λειτουργίες παίζουν καθοριστικό ρόλο στη λήψη αποφάσεων της καθημερινής ζωής, μειωμένες επιτελικές ικανότητες (συμπεριλαμβανομένων του σχεδιασμού, της γνωστικής ευελιξίας και της ικανότητας λογικής σκέψης) θα μπορούσαν να ερμηνεύσουν την αυξημένη συσσώρευση λίπους μέσω μακροχρόνιας υιοθέτησης λανθασμένων πρακτικών διατροφής και άσκησης.

Η συγκεκριμένη έρευνα εξέτασε τη σχέση ανάμεσα σε ανοσολογικές-μεταβολικές επιδράσεις της παχυσαρκίας και τη γενική γνωστική ικανότητα. Λαμβάνοντας δεδομένα από νέους και μέσης ηλικίας Έλληνες εθελοντές, οι οποίοι δεν παρουσίαζαν κλινικά ανιχνεύσιμα προβλήματα σχετιζόμενα με παχυσαρκία, η μελέτη είχε δύο βασικούς στόχους. Πρώτον, να διερευνήσει την πιθανή αρνητική συσχέτιση ανάμεσα στην παχυσαρκία και την ρέουσα νοημοσύνη χρησιμοποιώντας ένα μη λεκτικό τεστ επίλυσης λογικών προβλημάτων. Δεύτερον, να συγκρίνει δυο εναλλακτικά μοντέλα σχετικά με την κατεύθυνση της σχέσης παχυσαρκίας-νοημοσύνης, αξιολογώντας τη χρόνια χαμηλού βαθμού φλεγμονή ως διαμεσολαβητική μεταβλητή. Παράλληλα ελέγχθηκε η επίδραση ψυχολογικών παραγόντων (συμπτώματα κατάθλιψης και άγχους), τρόπου ζωής (άσκηση), και άλλων φυσιολογικών παραγόντων (δείκτες μεταβολικής δυσλειτουργίας).

Οι συμμετέχοντες στην έρευνα (199 άτομα) ήταν ελεύθεροι σοβαρών και χρόνιων αυτοάνοσων ή/και νοσημάτων του συνδετικού ιστού. Από αυτούς αποκλείστηκαν επιπλέον όσα είχαν ιστορικό παρουσίας ψυχολογικών, νευρολογικών διαταραχών ή/και κρανιοεγκεφαλικών κακώσεων. Ακόμα, άτομα με πρόσφατο ιστορικό λοίμωξης ή παρουσία λευκοκυττάρωσης δεν συμπεριλήφθηκαν στο τελικό δείγμα (N = 188).

Οι μετρήσεις που πραγματοποιήθηκαν περιελάμβαναν *α) γνωστικές, ψυχολογικές και μετρήσεις φυσικής δραστηριότητας*: το τεστ Γενικής Νοητικής Ικανότητας Ενηλίκων (General Ability Measure for Adults, GAMA), μια μη λεκτική δοκιμασία επίλυσης λογικών

προβλημάτων που αξιολογεί τη γενική νοητική ικανότητα και ειδικότερα την ρέουσα νοημοσύνη, η κλίμακα Κατάθλιψης του Beck II, η κλίμακα Ιδιοσυγκρασιακού Άγχους του Spielberger, και το ερωτηματολόγιο σωματικής δραστηριότητας Godin *β) Σωματομετρικοί δείκτες*: ο Δείκτης Μάζας Σώματος (Body Mass Index, BMI, βάρος/ύψος^2), ο λόγος περιφέρειας μέσης/ισχίου (waist-/hip-circumference, WHR) καθώς και το συνολικό ποσοστό λίπους σώματος (body fat percent, BF%) στο σώμα *γ) βιοχημικοί δείκτες*: C-αντιδρώσα πρωτεΐνη (hs-CRP), ινωδογόνο, ταχύτητα καθίζησης ερυθρών αιμοσφαιρίων (ΤΚΕ), αντίσταση στην ινσουλίνη με βάση το μοντέλο ομοιόστασης HOMA-IR και ολική αδιπονεκτίνη ορού.

Οι συμμετέχοντες εντάχθηκαν σε τρείς ομάδες: νορμοβαρείς (BMI: 18.5-24.99), υπέρβαροι (BMI: 25-30) και παχύσαρκοι (BMI: ≥30), ενώ για τον καθένα υπολογίστηκε ένας συνολικός σωματομετρικός δείκτης παχυσαρκίας (βασιζόμενος στους BMI, WHR, BF%) καθώς και ένας συνολικός δείκτης φλεγμονής (hs-CRP, ΤΚΕ, ινωδογόνο).

Όπως ήταν αναμενόμενο οι τρείς ομάδες διέφεραν σημαντικά ως προς τους σωματομετρικούς, φλεγμονώδεις, μεταβολικούς δείκτες και τη συγκέντρωση αδιπονεκτίνης, με τα παχύσαρκα άτομα να παρουσιάζουν υψηλότερες τιμές σε σχέση με τους νορμοβαρείς και τους υπέρβαρους σε όλους τους παραπάνω δείκτες, με εξαίρεση φυσικά την αδιπονεκτίνη όπου παρατηρήθηκε η αντίστροφή τάση. Δεν βρέθηκαν διαφορές ως προς τις βαθμολογίες στις κλίμακες κατάθλιψης, άγχους και σωματικής δραστηριότητας καθώς και ως προς τον δείκτη συνοσηρότητας.

Οι αναλύσεις σε σχέση με τη γνωστική ικανότητα έδειξαν ότι οι παχύσαρκοι συμμετέχοντες παρουσίασαν σημαντικά χαμηλότερη επίδοση στο τεστ επίλυσης λογικών προβλημάτων συγκριτικά με αντίστοιχους ηλικιακά νορμοβαρείς και υπέρβαρους, ακόμα και ελέγχοντας ως προς τις μεταβλητές της κατάθλιψης, του άγχους, της σωματικής

δραστηριότητας και τους μεταβολικούς δείκτες (ινσουλίνη, HOMA-IR, αδιπονεκτίνη). Τα ποσοστά των συμμετεχόντων με εκτιμώμενο δείκτη ρέουσας νοημοσύνης εντός φυσιολογικού εύρους υπολογίστηκαν σε 90%, 88% και 78% για τους νορμοβαρείς, τους υπέρβαρους και τους παχύσαρκους, αντίστοιχα. Οι υπόλοιποι συμμετέχοντες παρουσίασαν βαθμολογίες στο φάσμα της οριακά χαμηλής επίδοσης (70-85 βαθμοί).

Επίσης διερευνήθηκαν δύο εναλλακτικά μοντέλα δομικών εξισώσεων, με το πρώτο να υποθέτει μια άμεση επίδραση της παχυσαρκίας (συνολικός σωματομετρικός δείκτης) στη γνωστική ικανότητα (GAMA) ενώ το δεύτερο μοντέλο υπέθετε την αντίστροφη σχέση, με τη μειωμένη γνωστική λειτουργία να είναι αυτή που οδηγεί σε αύξηση του BMI. Κάθε μοντέλο περιελάμβανε μια σειρά από παράλληλες διαμεσολαβητικές μεταβλητές (ψυχολογικοί παράγοντες, σωματική δραστηριότητα, δείκτες μεταβολικής δυσλειτουργίας) και εξέταζε τόσο άμεσες όσο και έμμεσες επιδράσεις ανάμεσα στην παχυσαρκία και την γνωστική λειτουργία. Το πρώτο μοντέλο παρουσίασε σημαντικά καλύτερη προσαρμογή στα δεδομένα σε σύγκριση με το δεύτερο.

Επομένως, με βάση τα αποτελέσματα φάνηκε ότι υπάρχει μια αντίστροφη σχέση μεταξύ αυξημένου BMI και ρέουσας νοημοσύνης, με τους παχύσαρκους να παρουσιάζουν σημαντικά χαμηλότερη επίδοση σε σχέση με ηλικιακά εξομοιωμένα νορμοβαρή και υπέρβαρα άτομα. Ακόμα πιο σημαντικό είναι ότι η σχετιζόμενη με την παχυσαρκία χρόνια χαμηλού βαθμού φλεγμονή φαίνεται να συσχετίζεται άμεσα με τα γνωστικά ελλείμματα, ανεξάρτητα από μεταβολικούς (π.χ. αντίσταση στην ινσουλίνη, επίπεδα αδιπονεκτίνης), ψυχολογικούς παράγοντες (συμπτώματα κατάθλιψης και άγχους) αλλά και τη σωματική δραστηριότητα.

Πλέον, γίνεται ολοένα πιο αποδεκτό ότι οι αρνητικές επιδράσεις της παχυσαρκίας στη γνωστική ικανότητα ανακύπτουν πολύ νωρίτερα από ότι πιστεύαμε στο παρελθόν και

δεν διαμεσολαβούνται αποκλειστικά και μόνο από τις τυπικές κλινικές συνέπειες της, όπως η υπέρταση, ο διαβήτης και η αρτηριοσκλήρυνση. Αντίθετα, μπορεί να προκύπτουν από πολύ πιο πρώιμες παθοφυσιολογικές συνέπειες ενδογενών ανασολογικών διεργασιών που σχετίζονται με την παχυσαρκία. Αυτές με τη σειρά τους ενδεχομένως να έχουν άμεσες βλαπτικές συνέπειες στον κεντρικό νευρικό σύστημα.

Η συχνότητα εμφάνισης της παχυσαρκίας στην Ελλάδα αυξάνεται με ανησυχητικό ρυθμό, τόσο σε ενήλικες όσο και σε παιδιά. Το γεγονός αυτό εγείρει σοβαρούς προβληματισμούς όχι μόνο για την ανάπτυξη των τυπικών ιατρικών προβλημάτων που σχετίζονται με την παχυσαρκία, αλλά και την εμφάνιση γνωστικών δυσλειτουργιών, με πολύ πιθανή την μελλοντική σοβαρή αύξηση των ποσοστών επιπολασμού άνοιας πρώιμης έναρξης στον ελληνικό πληθυσμό.

Obesity, Chronic Low-Grade Inflammation and Cognition Impairment

1. Introduction

1.1 Obesity

Survival of organisms crucially depends on food intake. For millennia man strived through a hostile environment walking miles to forage and ensure this precarious prerequisite of life. As brief periods of nutrient sufficiency alternated with prolonged periods of famine, evolution developed mechanisms to store energy in presence of food increasing survival chances during its absence.

However, as our dietary entourage changed over time, the evolutionary benefits of nutrient storage adversely rebound. Mainly from the industrial revolution onwards, availability of food and ease of access progressively increased. A consequent gradual rise of mean body weight and limitation of the population proportion that lived under conditions of malnutrition (at least in the developed countries) followed. This decisively contributed not only to improvement of survival rates but also productivity, thus busting social progress. The rising trajectory of mean weight was sustained throughout 19th century, as well as the 20th. At this time point, conjointly with medical advancements both on preventive and therapeutic level, the plateau of genetic limits for height growth was reached and so immoderate weight gain started gaining ground. In the last decades, weight gain as a consequence of sustained overnutrition galloped forming worldwide an epidemic of obesity.

Definition, classifications and basic assessment indices

Obesity is characterized by *abnormal or excessive accumulation of fat, the basic unit of nutrient energy storage, at an extent that constitutes a health hazard*[1]. It was recognized as a disease and consequently included in the International Classification of Diseases (ICD) by

the World Health Organization (WHO) in 1948, the exact year that the organization was established. This fact emphasizes the importance of the obese and overweight condition as a threat to global health. In the current 10th ICD edition, obesity holds code E66 under chapter IV, which is dedicated to endocrine, nutritional and metabolic diseases[2]. The disability and shortened life span associated with it are consequences of a wide spectrum of medical co morbidities, and so obesity constitutes a major risk factor for at least two of the four main non communicable diseases (NCDs) according to WHO: diabetes and cardiovascular disease[3]. Quantification of overweight and obesity states is usually based on the Body Mass Index, which corresponds to the quotient of an individual's subject body weight in kilograms to the square of his/her height in meters.

$$BMI = (\text{weight in kg})/ (\text{height in m})^2$$

For example, the BMI of an adult who weights 65kg and whose height is 1.70, is 22.5.

$$BMI = 65kg/(1.70)^2 = 65/2.89 = 22.5\ kg/m^2$$

Based on the degree at which health complications and morbidity are associated to obesity[1], WHO has set BMI cutoffs to classify underweight, normal weight, overweight and obesity in adults (figure 1). According to them, a person with BMI under 18.5 is considered underweight, a BMI of 18.5 to 24.9 indicates optimal weight, a BMI equal or greater than 25 constitutes overweight, while a BMI equal or greater than 30 falls into the obese category[4].

Due to its ease of use (requires only a balanced beam scale for weight measurement and a non-stretchable measuring tape for height measurement) and simplicity (quick calculation that produces a single, easily conceptualized numeric result), BMI is one of the most widely used indicators of excess weight. The fact that its values apply to both sexes and are age-independent, at least for adults[4], also adds to its merit. Accordingly BMI is used in a variety

of contexts, including clinical practice for individual diagnosis, calculation of ideal weight and set of medical goals[5].

	BMI (kg/m^2) cut–off points		
Classification	**Principal**	**Complications risk**	**Additional points of health action**
Underweight	<18.50	Low (but risk of other health problems increased)	
Severe thinness	<16.00		
Moderate thinness	16.00 - 16.99		
Mild thinness	17.00 - 18.49		
Normal range	18.50 - 24.99	Average	
Overweight	≥25.00		≥23.00 (for populations of smaller statue e.g. Asian, health complication risk is increased at 23kg/m^2 instead of 25kg/m$^{2)}$
Pre-obese	25.00 - 29.99	Increased	
Obese	≥30.00		≥27.50
Obese class I	30.00 - 34.99	Increased (moderate)	
Obese class II	35.00 - 39.99	Increased (severe)	32.50
Obese class III	≥40.00	Increased (extremely severe)	37.50

Figure 1. International BMI cut-off points for the classification of adults as underweight, overweight or obese and relative corresponding complications risk. Additional points for

public health action, taking into account populations of smaller statue (e.g. Asian populations). Adapted from WHO[1,4].

However, as this index was originally developed for population studies[6], it does not take into account body composition, thus factors such as muscle content/weight, bone density, cartilage, body hydration and most importantly fat proportion are not taken into account. For example highly trained athletes with limited fat percentage yet high weight due to overdeveloped muscle tissue may be characterized as overweight or even obese based on their BMI (figure 2). On the other hand, this index could also be misleading for children and elderly, who might be falsely classified as underweight due to fluctuations in bone density and consequently to variable ratio of bone to total weight[7].

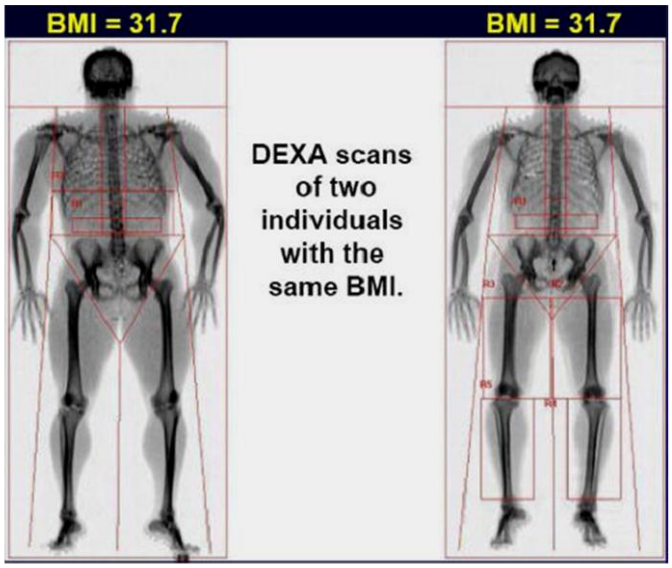

Figure 2. Differences in fat mass quantity between two individuals of the same BMI.

Another limitation of BMI cutoffs is that they were developed using Caucasian population standards[6]. Moreover, it is known that the health consequences of obesity are related more closely to fat accumulation than to overall weight[8]. It was therefore argued that BMI cut off points may underestimate health risks faced by certain populations of bigger (e.g. native Australian Aboriginals population)[9] or smaller (e.g. east Asian populations)[10,11] stature, given that different ethnic groups do not share the same body fat composition. Taking into account those concerns, WHO convened an Expert Consultation, which concluded that the current WHO BMI cut off points should be retained as an international classification system, but should be used along some additional "points of public health action" (points of 23, 27.5, 32.5, and 37.5 kg/m^2; figure 1). Hence meaningful comparisons of fat accumulation within certain populations but also between divergent populations are still feasible[12].

Overall, despite its limitations BMI remains a crude but valuable mean for assessing obesity, allowing identification of increased morbidity risk and intervention priorities, primarily at the population level and secondarily in individual patients. BMI data also facilitates the creation of a sound basis for evaluation of interventions implemented for prevention and management of obesity[1].

Another crucial aspect that BMI fails to address is *body fat distribution*. It is well known, that the disorders associated with obesity do not solely and linearly relate to total quantity of excess fat but more importantly to its dispersion through the body[13,14]. Significant fat accumulation can be present both subcutaneously and viscerally, enveloping the internal organs (figure 3).

Body fat centralization is an aggravating risk factor on its own account and individuals with surplus in the abdominal depots have consistently been found to be more susceptible

to the deleterious metabolic consequences of obesity compared to those with higher proportions of subcutaneous fat accumulation[13,14]. Therefore, a distinction between two types of obesity is useful: a) the more "dangerous" *visceral* or *abdominal obesity*, characterized by fat buildup in the trunk (especially around the waist not only subcutaneously but also intraperitoneally) and b) the metabolically less "threatening"

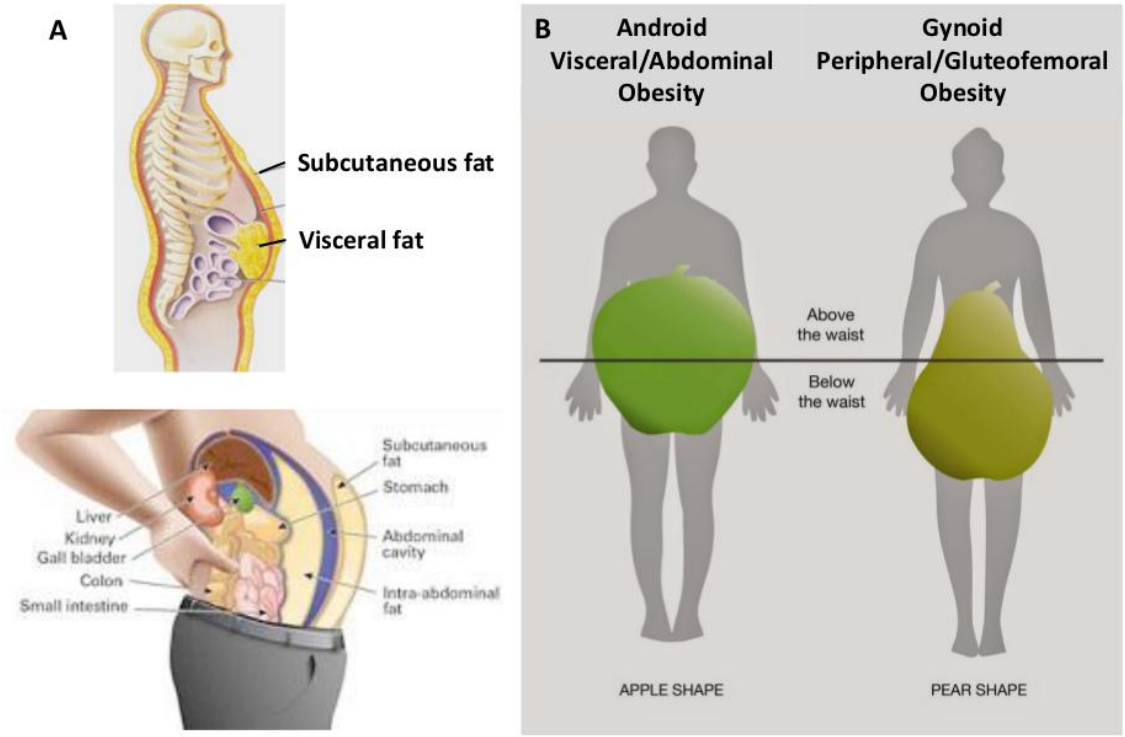

Figure 3. Subcutaneous and visceral fat accumulation (A) and typical distribution of android and gynoid fat (B).

peripheral or gluteofemoral obesity, which is distributed more circumferentially and uniformly throughout the body, wherein fat is mostly found bellow the skin in the gluteal and femoral regions[15]. Those two anatomically based classifications of obesity are also referred to as *android* and *gynoid* obesity, respectively, suggesting that the first form is preponderant in men and the latter in women, although the two types may occur in both

sexes[16]. As shown in figure 3, android or “apple” shape obesity is heavily localized above the waist while gynoid or “peach” shape obesity below the waist. Estimation of body fat centralization is therefore important and clinical practice relies on two measurement indices:

a) *Waist-to-hip ratio* (WHR): Values above 0.90 for men and 0.85 for women indicate excess abdominal fat and are defined as cut off criteria for the diagnosis of Metabolic Syndrome (MetS) according to WHO[17]

b) *Waist circumference*: National Cholesterol Education Program (NCEP) of National Institutes of Health (NIH, USA) guidelines state that waist circumference should be measured at the top of the iliac crest and values greater than 102 cm for men and 88 cm for women are considered to be a significant indicator of abdominal obesity and a basic criterion for metabolic syndrome (MetS) diagnosis[18]. The International Diabetes Federation (IDF) further lowers those values for men and also takes into account populations geographic characteristics. Thus, for men and women of European origin the cut off points are set at >94cm and >80cm respectively, while for South Asians, Chinese and Japanese are set at >90cm and >80cm respectively[19,20]. Use of those two indices is complementary to BMI and provides additional information for the estimation of metabolic risks stemming from obesity.

There are various other tools, apart from the anthropometric assessment methods previously presented, that are useful for measuring body fat in certain clinical situations and in obesity research. Obese individuals can be characterized by measuring body composition, anatomical distribution of fat, energy intake, and insulin resistance, among others. A list of those characteristics of obesity considered suitable for measuring in genetic studies also, have been agreed and summarized in figure 4[21]. Measures in a given category are not necessarily of equal validity.

Characteristic of obesity measured	Examples of measurement tools
Body composition	BMI; Waist Circumference; Underwater weighting; dual-energy X-ray absorptiometry (DEXA); isotope dilution; Bioelectrical impedance; skinfold thickness
Anatomical distribution of fat	Waist circumference; WHR; Computer tomography; Ultrasound; Magnetic resonance imaging
Partitioning of nutrient storage	[^{13}C] palmitic acid; extended overfeeding challenge
Energy intake	"Total" by prospective dietary record or recall; "Macronutrient composition" by prospective dietary record or recall or by dietary questionnaire
Energy expenditure	"Total" by double-labeled water; "Resting" by indirect calorimetry; Physical activity level (PAL) by questionnaire; Motion detector; Heart-rate monitor, etc.

Figure 4. Aditional tools for the assessment of obesity. Source: WHO, 2000[21]

Epidemiology

Although obesity as a medically adverse condition is a relatively "young" problem, having appeared on the global health scene during the last 100 years, it has been escalating worldwide in accelerating rhythms. In 1997 WHO officially recognized obesity as a global threatening epidemic[1] and in the turn of the millennia a historic point in human evolution was reached, when the number of overweight adults exceeded for the first time ever the number of those characterized as underweight[22]. Up until mid 20th century, obesity was a health challenge affecting primarily high-income countries, mostly United States and central-north Europe[1]. Therefore obesity was considered a condition consequent to high socioeconomic status. In the last decades thought, a dramatic increase of obesity prevalence in populations of most middle-income and many low-income countries, such as Mexico, China and Thailand, has changed this perception[23,24]. Prevalence of obesity appears to follow a predictable rising pattern in those regions: At first it is the higher socioeconomic strata

living in urban areas that succumb to abnormal weight gain, but as a country's gross domestic product rises, this trend gradually reverses and the prevalence of obesity becomes higher in the low socioeconomic level and rural areas. It has been grossly estimated on the basis of cross-sectional and some longitudinal studies that obesity rates rose by as much as 60% in countries of intermediate development in the last ten years[23,24]. Countries with emerging economies, now more than ever face a "double burden": while infectious diseases and undernutrition still remain serious public health concerns, extensive exposure to low cost but energy-dense and nutritionally poor food has led to a simultaneous overweight and obesity rise[25].

The latest estimation of WHO in 2008 for global overweight and obesity reported 35% of the adult population being overweight and 11% obese. In absolute numbers, those figures correspond to 1.4 billion people exceeding normal weight limits, with more than 500 million of them being obese (over 200 million men and nearly 300 million women)[3]. However, in a more recent systematic analysis[26] continuous proliferation of obesity both in developed and developing countries provides an even more overwhelming illustration of the problem affecting adults globally. The number of overweight and obese individuals in 2013 reached 2.1 billion, an increase of 27.5% between 1980 and 2013. At the same period, male overweight and obesity combined increased from 28.8% to 36.9%, while respective proportions for women were 29.8% to 38.0%.

Additionally, the global map of obesity for men and women shows extreme values of obesity rates in Middle East and the island states of the South Pacific, with obesity exceeding 50% in men in Tonga and in women in Kuwait, Kiribati, Federated States of Micronesia, Libya, Qatar, Tonga, and Samoa (figure 6).

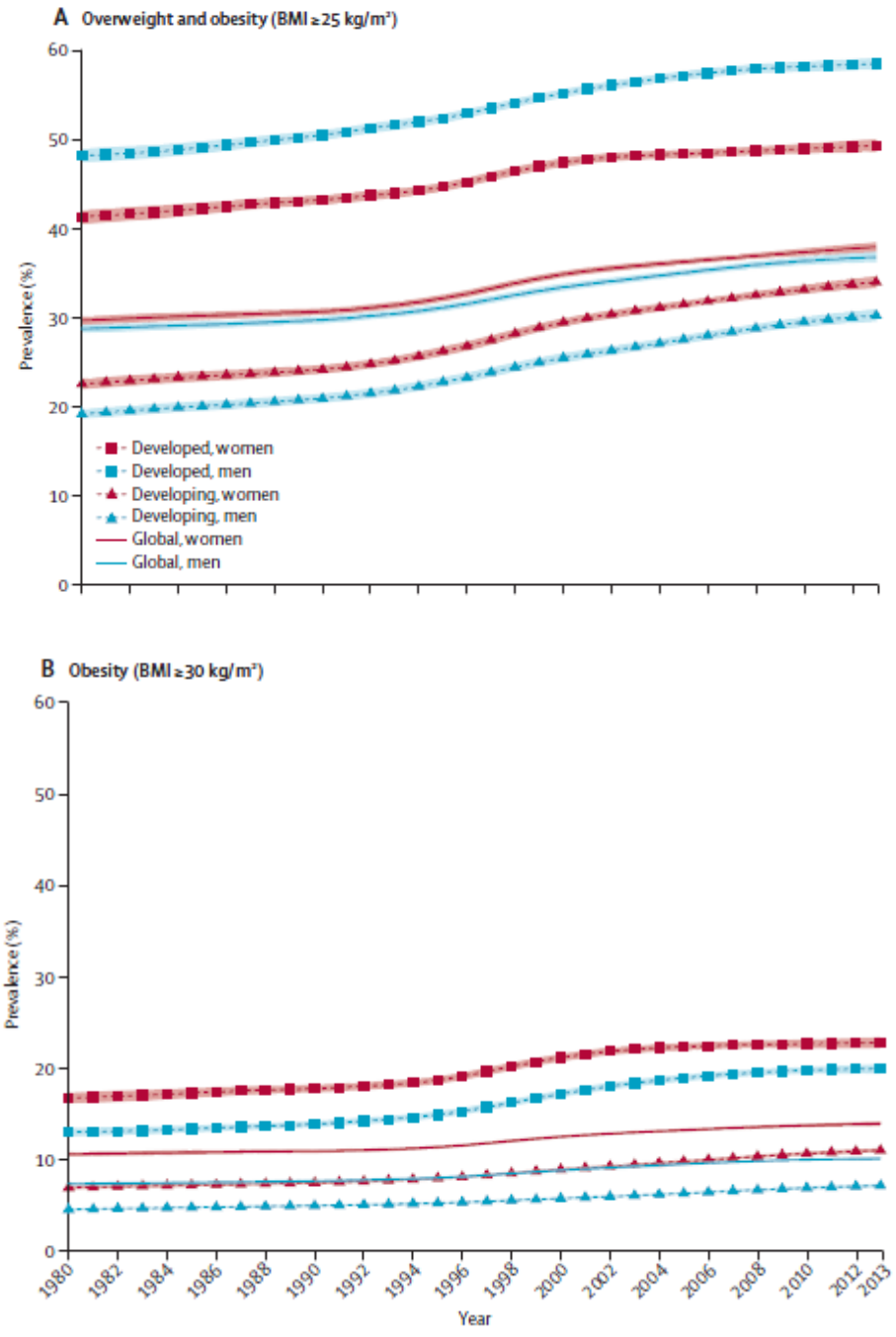

Figure 5. Trajectories of age-standardized prevalence of overweight and obesity and obesity alone by sex, for adults aged ≥20 years during 1980 to 2013. Source: Ng et al., 2014[26].

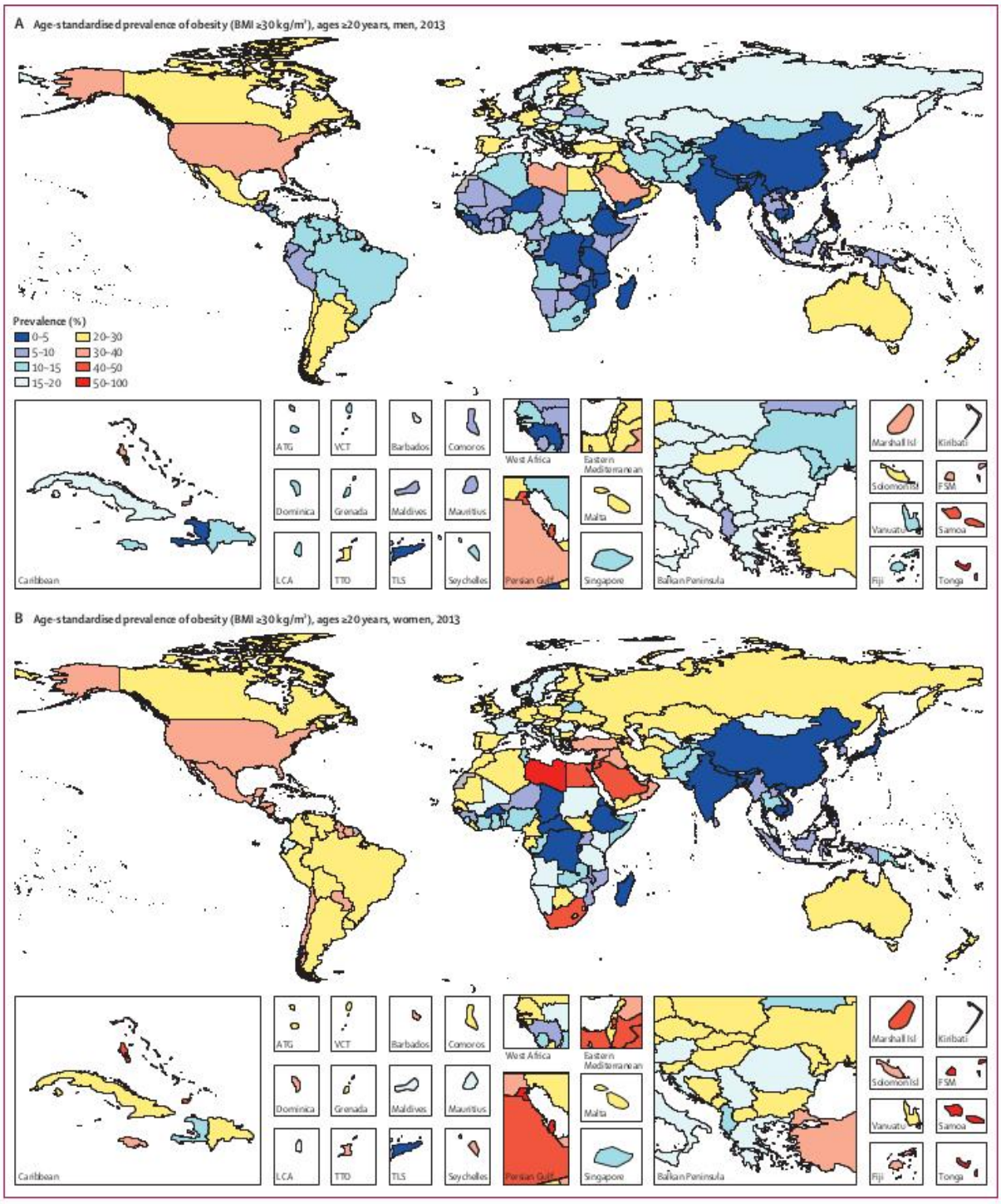

Figure 6. Global, age standardized prevalence of obesity (BMI ≥ 30kg/m^2), ages ≥ 20 years in men (A) and women (B) in 2013. Source: WHO, 2014[27].

While rates of obesity are on the rise in both developed and developing countries, last year the relative prevalence of obesity among women was higher than among men (figure 5). As shown by up to date data[28] from 10 member countries of the Organization for Economic Co-operation and Development (OECD), a frail stabilization of the overweight and obesity rates was noted in England, Italy and the United States, while there was a moderate increase in Canada, Korea and Spain. Still, taking into account that growth of obesity numbers remained vigorous in France, Mexico, Australia and Switzerland, and that currently more than one in three adults in Mexico, New Zealand, United States, and more than one in four in Australia, Canada, Chile and Hungary are obese, the epidemic seems far from restrained (figure 7).

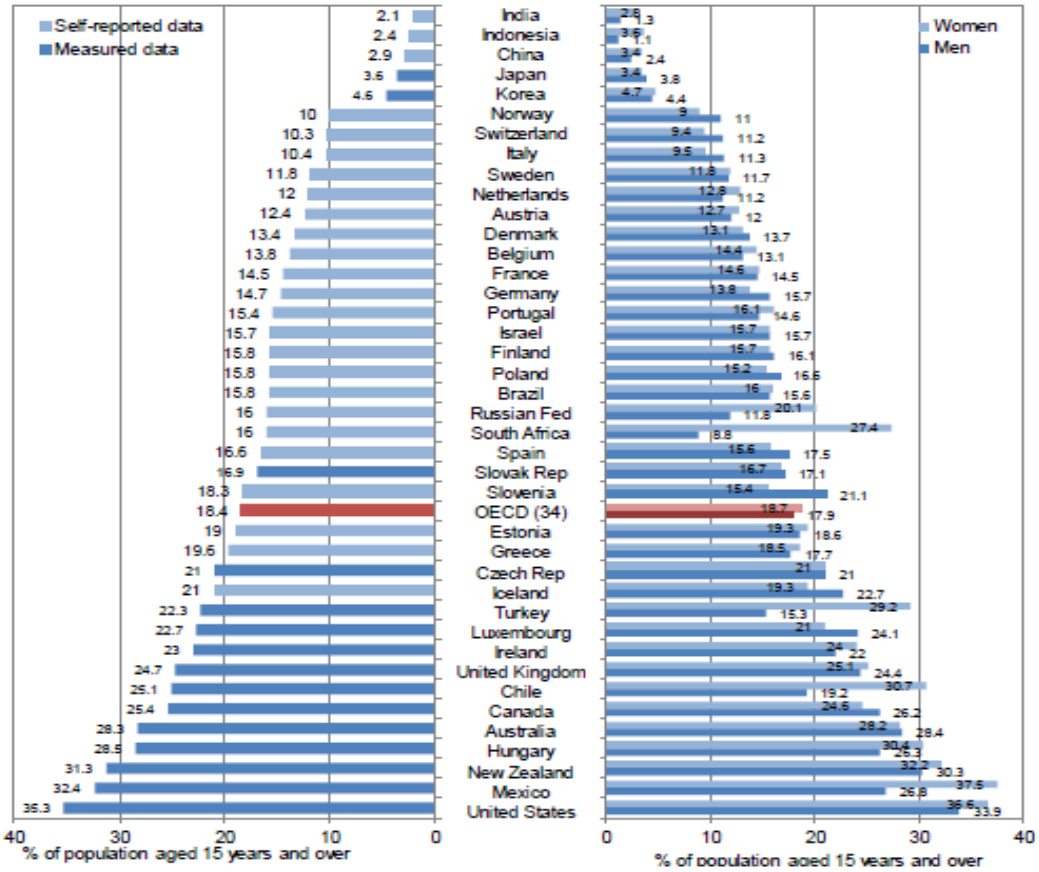

Figure 7. Adult obesity rates in Greece in comparison to OECD member-countries in 2012 or nearest year. Source: Organization for Economic Co-operation and Development, 2014[28].

Weight increase related problems do not only infiltrate ever more countries and lower economic layers but also ever younger ages. With rising childhood obesity rates it is estimated that over 170 million children can be classified as overweight or obese world-wide, including more than 40 million children under the age of 5[23]. Notably these rates are rising faster in developing countries. The percentage of overweight/obese boys and girls exceeds 30% in several western countries (figure 8) with numbers projected to reach 70 million by 2025[28].

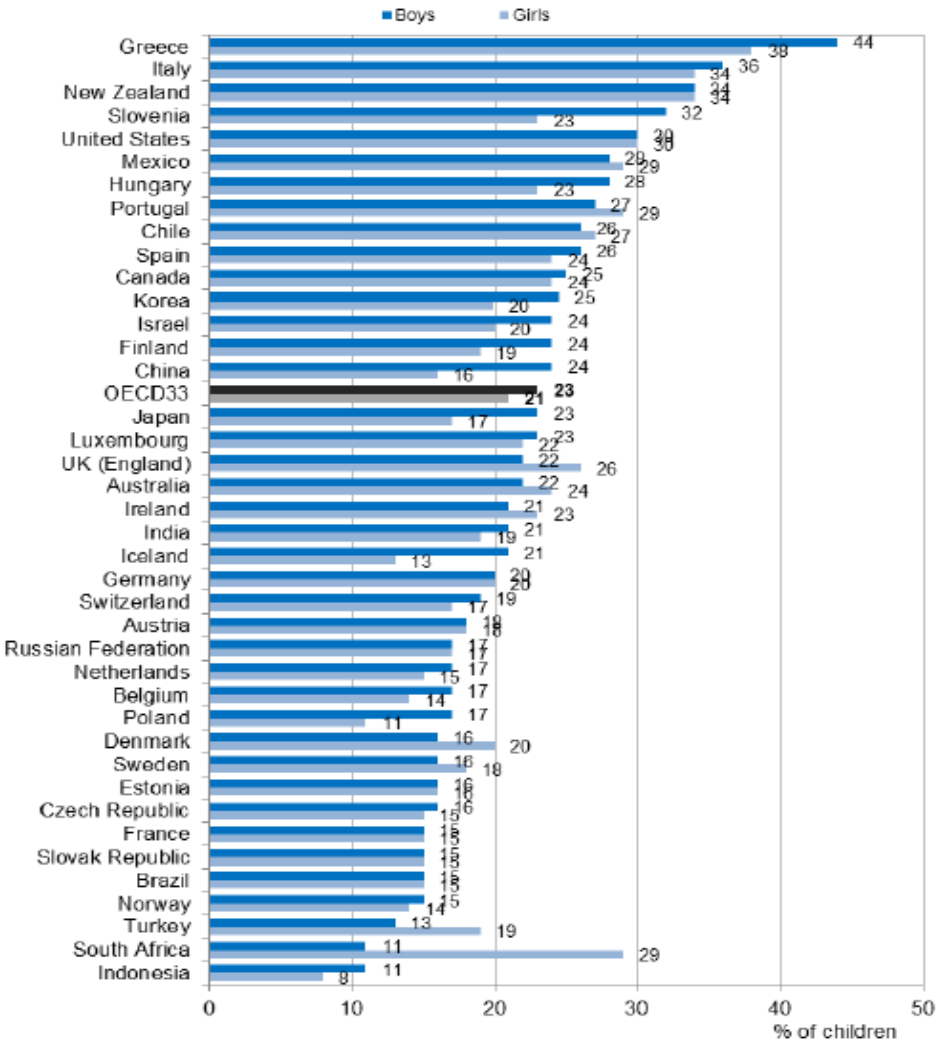

Figure 8. Childhood obesity rates (aged 5-17 years) in Greece in comparison to OECD member-countries in 2010. Source: Organization for Economic Co-operation and Development, 2014[28].

In Greece, although accurate recording and reliable nationwide data have only recently begun to emerge, obesity is also a serious public health problem. In the first national epidemiological research[29] conducted in 2003, overall prevalence of overweight and obese were 35.2% (41.1% in men, 29.9% in women) and 22.5% (26% in men, 18.2% in women), respectively. Men did not differ in obesity rates across ages, in contrast to women who showed a progressive tendency to higher BMI scores with increasing age. Interestingly, women exceeding abdominal obesity cut offs outnumbered men (35.8 vs. 26.6%, respectively), especially after menopausal age. A few years later in 2008, WHO estimations[30] for adult obesity (≥ 20 years old) in Greece revealed a much more aggravated picture for overweight (53.7% overall, 59.7% among men and 47.9% among women) and obese individuals (20.1% overall, 20.4% in men and 19.9% in women). Forecasts (2010-2013) in the same report were menacing, bringing the estimated percentage of obese individuals to 32% by 2020, and 42% by 2030.

Adolescent and childhood obesity present an even more ominous picture, with Greece ranking first in childhood obesity among OECD countries[28] (figure 8). According to WHO, 32% of 15 year-old boys and 14% of girls in 2010 were overweight, while for 13 year olds the corresponding numbers were 34% and 19%, respectively[31]. In the ages 1 to 12 years a recent meta-analysis[32] estimated prevalence rates of 23.7% and 10.2% for overweight and obese children.

Obesity causes

The term "obesity" derives from the Latin "obesitas", with its first component “ob” meaning a lot, excessively, and the second being the past tense “esus” of the verb “edere”,

meaning to eat, to nourish. Therefore, this etymological interpretation describes the first part of the basic mechanism that gives rise to obesity development: excessive food intake. Along with its second part, low energy expenditure, a fundamental concept for obesity emerges: energy equilibrium (figure 9), which states that maintenance of a stable weight status depends on the long-term balance of those two parameters[33].

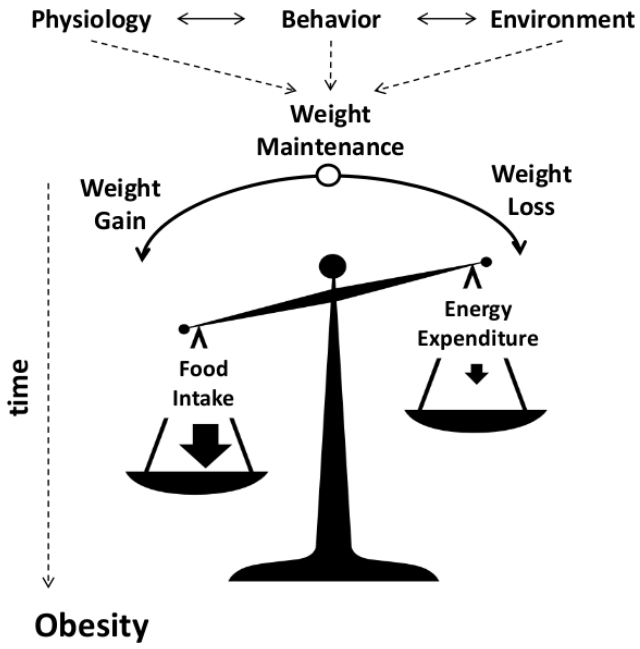

Figure 9. Energy equilibrium. Adapted from Knecht, 2008[34].

Although, this interpretation is biologically true, we now know that obesity is a much more complex condition than lack of self control in food consumption and low compliance to recommendations for daily physical activity[33]. In agreement with our evolutionary past of scarce nutrient availability, endocrinological advancements have shown that in order to increase survival chances, human organism has evolved a tendency for energy hoarding i.e. the hypothalamic mechanisms regulating appetite and satiety, favor appetite and the

orexiogenic nuclei of the hypothalamic arcuate nucleus are more potent than the anorectic ones. With this in mind, the recent tremendous changes in our nutrient environment become even more important determinants of the energy balance dysregulation.

Ease of access and widespread availability of food is a contemporary reality exposing the individual to continuous stimuli for food consumption. However, the ensuing high frequency of meals is not always associated with adiposity increase[35]. It is the nutrient quality of food consumed, believed to contribute much more to obesity development with trans fats, refined carbohydrates and low fiber content increasingly being part of the dietary choices of modern people. This is part due to the high palatability of this type of food, a fact often depicted in the preference for away-from-home snacks over full meals. It is also important that high-caloric meals do not trigger the stomach satiety reflexes in contrast to diets of high fiber content like the Mediterranean diet. Food industry and advertisement strategies further favor such unhealthy dietary options, as processing which typically overloads such food with “hidden” fat, salt and/or sugar, increases their market value (e.g. potato chips sell for much more than potatoes). Furthermore, there is an increase in the food quantity consumed per meal, evident especially in the US food market with larger sizes of products available in supermarkets, bigger portions in restaurants, even bigger portions in home with steadily increase in the surface of the average dinner plate[36–38]. Overall, all of this external factors contribute to a dramatic increase in caloric intake[39].

On the other hand energy output is decreased. Contrary to common belief, extensive consumption of calories through physical activity is difficult and the modern sedentary lifestyle of mechanization and automation have sharply reduced even further the amount of energy required to spend in basic survival activities, work and entertainment. In most developed countries, working patterns augment long engagement with computers and

increase dependency on prepared food, usually purchased and not prepared at home, while built environment encourages long commutes, car use instead of walking and restrict leisure time and space for outdoor physical activity[24]. Stress and sleep deprivation, common characteristics of the westernized life style also add up in weight up gain. Moreover, addiction on TV and online social networking from an early age, has been found to keep people indoors, creating a fertile ground for obesity development[27]. Longer life span (rate of calorie consumption decreases with age advancement) and further spreading of westernized lifestyle in more and more cultures promote global obesity rates rise.

Of course genetic factors are not to be overlooked. Whole families are affected by obesity and chances are that a child with one or even worse both parents being obese, is also going to grow obese[40]. Familial predisposition is certainly reinforced by adoption of unhealthy dietary and sedentary patterns that might prevail within a family. Finally, many diseases and syndromes phenotypically result in increased adiposity e.g. Prader-Willi syndrome, while certain drugs may also enhance weight gain such as for example old type contraceptives, antidepressants or steroids.

Overall, obesity can be conceptualized as a failure of innate metabolic control mechanisms to counteract an overwhelmingly food abundant and life-sedentary promoting environment[41].

Medical consequences of obesity

An exhaustive body of literature links overweight status and obesity to premature death and serious morbidity. Around 3.4 million deaths annually are attributable to increased body weight, more than those attributed to insufficient nutrition. With an estimated overall reduction of life expectancy by 8 to 10 years[42], and an approximately 30%

increase of premature death risk for every 15 kilograms of excess weight gain[28], obesity has been ranked as the sixth largest cause of death and disability-adjusted life years (DALYs; sum of years lived with disability and years of life lost) after considering the independent effects of 67 different risk factors[43]. The earlier the onset and the greater the severity of obesity, the greater the risk for co-morbidities to emerge.

The most life-threatening chronic conditions associated with raised BMI are Diabetes Mellitus Type 2, cardiovascular disease and associated conditions, resulting mainly in stroke, ischemic heart disease and certain types of cancer, especially hormone dependent cancers[27].

Diabetes Mellitus Type 2 (T2DM) and prediabetes: BMI exceeding normal cut offs, central adiposity and rapid weight gain consist major factors for T2DM development[44]. The last decades, diabetes prevalence is in constant growth[45] and while in 2013 382 million people suffered from the condition, the number is projected to reach 592 million by 2035[46]. Diagnostic criteria include physical symptoms, such as polyuria, polydipsia and unexplained weight loss, in addition to one of the following: a random venous plasma glucose concentration >11.1 mmol/l or a fasting plasma glucose concentration >7.0 mmol/l (whole blood >6.1mmol/l) or two hour plasma glucose concentration > 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test or an Haemoglobin A1c (HbA1c) of >48 mmol/mol (6.5%)[47].

Dyslipidemia, in particular diabetic dyslipidemia, which is characterized by elevated levels of triglycerides, reduced high-density lipoprotein (HDL) cholesterol concentration and a change towards small dense low-density lipoprotein (LDL)[48]. Dysilipidemia[49], constitutes a leading risk factor for the development of cardiovascular disease (CVDs)[48].

Hypertension, defined as persistent resting systolic/diastolic blood pressure ≥140/90 mmHg[50] is closely related to obesity[51,52] and unsurprisingly follows a parallel upward trend,

affecting more than a quarter of the world's adult population in 2000, while a 30% increase in prevalence until 2025 is predicted[53].

Cardiovascular diseases include cerebrovascular disease, peripheral arterial disease (PAD) and coronary heart disease (CHD)[54]. In particular, CHD incidence in obese individuals is almost 50%-70% greater over 3- to 14-year periods than in normal-weight persons[55]. However the connection between central adiposity and CHD is multifactorial and thus complex. According to some investigators their link is mediated by raised rates of diabetes, hypertension and dislipidemia, whereas others emphasize the direct, independent impact of obesity[56–58]. In line with the latter, the American Heart Association has classified obesity as an independent major risk factor for CHD[59].

Metabolic syndrome (MetS) comprises a constellation of risk factors, whose co-occurrence exponentially increases the probability of developing CVDs and diabetes[60]. Abdominal obesity holds a crucial role in the diagnosis of the syndrome, which requires the presence of at least two of the following signs: elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low high-density cholesterol (HDL) levels[61,62].

Cancers: there is also a possible association of excess body fat with *certain types of cancer*, mainly endometrium, breast, renal and colon cancer[63].

Non alcoholic steatohepatitis (NASH): Increased fat deposition in the liver due to obesity might lead to a spectrum of hepatic abnormalities, ranging from isolated steatosis (triglyceride accumulation) to steatohepatitis (steatosis with inflammation, i.e. NASH), steatofibrosis, which sometimes leads to cirrhosis, hepatic failure and hepatocellular carcinoma[64]. NASH prevalence in the general population is 2.1-6.3%, rising to 9-40% in obese individuals and following the obesity epidemic, constantly gains ground as a causing factor of hepatic cirrhosis[65].

Non-lethal but aggravating health conditions associated with obesity also include:

Obstructive Sleep Apnea (OSA): Obese patients are at increased risk of sleep apnea, in which the transient occlusion of the upper airways leads to episodes of shallow breathing or pauses in breathing. The interrupted nocturnal sleep leads to poor sleep quality, daytime sleepiness, headaches, hypertension and finally to pulmonary hypertension and right heart failure. Diagnosis is based on findings of a sleep study and classified as mild (5 to 14.9 events/sleep hour), moderate (15 to 29.9 events/sleep hour) and heavy (> 30 events/sleep hour)[66].

Osteoarthritis and musculoskeletal problems: Supportive joints, especially in the knee, hip and lumbar spine, are overloaded as a result of increased body weight. Stress progressively wears the joints off, causing pain and loss of function, leading to the development of osteoarthritis and low back pain in younger ages and at greater degree of deterioration in comparison to normal weight population[67].

Other health problems that obese patients are more likely to develop are gallbladder disease, lymphedema, gastroesophageal reflux disease, prothrombotic state, incontinence, erectile dysfunction, infertility[68,69], menstrual disorders, and increased risk of complications during pregnancy and delivery[70].

1.2 Cognition and obesity

Obesity impacts all organs of the human body and brain is not an exception. Thus, apart from the well-known obesity comorbidities, a relatively new aspect of its adverse effects is increasingly gaining research interest: compromised neurocognitive function.

Cognition and its main domains

Cognition encompasses several psychological functions including all aspects of perception, thought, language, and memory[71]. The study of such a complex and multifactorial concept is facilitated by its division into different domains, each accessed through a wide variety of neuropsychological tests. The following presentation complies with the categories suggested by Lezak[72] and Straus[73], both well recognized references within clinical neuropsychology.

General cognitive performance: a crude picture of global cognitive function assessed mostly by brief dementia screening tests (e.g. Mini Mini Mental State Examination).

Memory: Long term or secondary memory (storage and retrieval of information over a long period of time*)* and short-term or primary memory (temporarily recall of information currently at use). Episodic (memorization of personal experiences and specific events in their spatio-temporal context) and semantic memory (general factual knowledge e.g. meanings, concepts, historic events).

Working memory: a component of primary memory, yet a wider concept referring to the ability to retain a small amount of information in mind in an active, readily-available state in order to perform mental operations.

Language: confrontational word retrieval (naming ability), receptive vocabulary (word meaning consolidation) and verbal fluency (ease and quantity of spontaneous speech production under semantic and phonemic constrains).

Attention: sustained (ability to focus and remain receptive over a continuous time period), selective (blocking of irrelevant to the task at hand stimuli) and divided (efficient use of attentional resources in order to attend simultaneously multiple tasks).

Psychomotor performance and speed: ability to coordinate sensory perception, cognitive process and fine motor coordination performance.

Visuo-spacial perception and spatial construction: organization and interpretation of sensory information enabling perception of the environment or recreation of designs.

Finally, *executive function* is an umbrella term that encompasses a diverse range of self-regulatory cognitive processes that supervise and coordinate other cognitive sub-processes (e.g. memory, language, motor functions) in order to adaptively respond to novel situations through complex goal-directed thought and action[74]. Importantly, working memory and attention have also been suggested to be part of the central executive[75,76]. Such presumed, higher order cognitive functions include[77]:

Inhibition, the capacity to suppress, when required, automatic, habitual responses that are considered inappropriate in a given context and impede other desired behaviors. Cognitive tests such as Stroop or Go No-Go tasks challenge this ability.

Mental flexibility or shifting, that involves rapid and flexible switching from one cognitive or behavioral strategy to another as required in the Trail Making Test part b or the computerized Attention Two Strategies.

Fluid reasoning and *problem solving*, referring to the ability to use abstraction, demonstrate flexibility and invent novel strategies to form concepts, as well as employment

of critical evaluation and selection of a sequences of actions in order to reach a specific goal**.** Tower of London task is an example of assessing this executive domain.

Decision making and delay discounting, encapsulates the ability to choose the best possible solution or action from a range of alternatives that present a degree of risk, while in position to dynamically update decisions according to new information being available. Delay discounting refers actually to the reward sensitivity of an individual and the degree of immediate rewards outweighing delayed larger gains, a constituent underpinning decision making.

Regarding their neuroanatomical substrate, executive functions are believed to be largely mediated by frontal brain regions, in particular the prefrontal cortex, although in connection with various other regions of the brain such as the parietal lobes, the basal ganglia and other subcortical structures[78]. Impairments in executive functions are manifested as poor judgment, difficulties in planning and managing everyday problems, inattention, lack of motivation, limited ability to control impulses, euphoria, echopraxia or echolalia etc. Severe deficits in those functions may comprise a "dysexecutive syndrome" and may be encountered in a wide facet of psychiatric and neurological disease entities (e.g. Attention Deficit Hyperactivity Disorder [ADHD], autism, schizophrenia, major depression etc.)[79,80].

Executive function and especially working memory, closely relates to yet another concept addressed within neuropsychological evaluation: *fluid intelligence (Gf)*. As opposed to *crystallized intelligence (Gc)*, which is the ability to utilize one's knowledge and skills accumulated through lifetime experience and learning processes[81], Gf is the capacity to reason, decipher novel situations and abstract information through identification of underlying patterns and relationships, and to generate solutions independently of previously

acquired knowledge[81]. Gf includes inductive and deductive reasoning and along with Gc constitute general intelligence (g)[82], sometimes also mentioned as intellectual functioning, a construct purporting to measure hypothesized global cognitive ability[72]. Frontal lobe function has also been implicated in Gf, with frontal lobes integrity being an important key element for successful performance in related tasks[83], in contrast to measurement of crystallized intelligence where involvement of frontal lobes seems neither more nor less than that of the other lobes[84] Undoubtedly, executive function, working memory and Gf are highly correlated[85], a fact that has given rise to suggestions that they are actually identical concepts[86], thought such arguments have been opposed by other researchers [85,87–89].

Cognition and medical consequences of obesity

Obesity induced medical pathologies, especially cardiovascular risk factors such as T2DM, hypertension and dyslipidemia were early recognized as major causative pathways leading to cognitive degradation and dementia[90–93]. Hence, their role as generators of or contributors to cognitive impairments related to raised BMI has been extensively studied.

Type 2 Diabetes Mellitus: Results from the vast majority of relevant large-scale longitudinal studies agree that diabetes significantly increases the risk of cognitive decline and dementia in late life[94,95], with Alzheimer's disease being the predominant type (e.g. 91%[96], 82.5%[97]) and Vascular dementia following[98]. Retrospective analyses of the probability of developing dementia among diabetics in comparison to healthy persons estimate a two to three-fold risk increase[97,99] while impaired fasting glucose and diabetes has been associated with Mild Cognitive Impairment (MCI)[97], which in itself is a significant risk for dementia[100]. In a systematic review of prospective studies, performance changes on cognitive tests over time for patients with diabetes were estimated between 1.2 to 1.5 times greater than the

comparison healthy groups[101]. Moreover, participants who were diagnosed in end-time-point assessments with cognitive decline, were 1.2 to 1.7 times[101] more likely to belong in the diabetic group at baseline than non-diabetics. Overall, diabetes was found to have a triple risk action with 1.5-fold greater risk for cognitive decline, a 1.2 to 1.5 faster rate of decline and 1.6-fold greater risk for dementia development[101]. Importantly, cognitive dysfunction has been linked with glycosylated hemoglobin index (HbA1c), an indicator of long term glycemic dyscontrol, not only in elderly[102] but in middle aged individuals as well[103]. Further research suggests that the increased risk of cognitive dysfunction is probably not mediated by the effects of diabetes on cardiovascular disease development[104]. Thus cognitive dysfunction may be evident long before the emergence of overt cardiovascular complications among adults with insulin resistance (pre-diabetes)[96,97] and among obese children with T2DM[105].

Learning and memory are the most frequently reported cognitive domains affected by T2DM-related factors in adults, unlike patients with type 1 diabetes that rarely present with such deficits[106]. Lower scores on mental and motor speed test, as well as executive tests have also been reported for T2DM patients in comparison to healthy adults, but it has been argued that such deficits are evident in younger ages (34-65 years old)[103], while the most commonly identified memory impairments associated with T2DM, especially in verbal memory, is manifested in patients over 60-65 years of age[107]. Unsurprisingly, in older populations nearly all cognitive domains seem to be at risk[108].

A wide range of endocrine, metabolic and vascular dysfunctions may explain the impact of diabetes on cognitive function, including neurotoxicity (glucose toxicity), changes in insulin and amyloid metabolism, increased oxidative stress, and chronic low grade inflammation diagnosed by an increase of several acute phase proteins including C-reactive

protein (CRP) as well as by the cytokines interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α)[106]. Nonetheless, a causal relationship still remains unclear and further research on the matter is warranted. Despite the well-established association, there is no firm data yet that glucose lowering treatment positively affects cognition in this population[109,110]. Albeit, there are some promising findings that antidiabetic therapy, especially oral therapy, may mitigate cognitive deficits[111].

Hyperlipidemia: Increased serum total cholesterol often accompanies obesity and is one of the key modifiable risk factors for CVDs. In most cross-sectional and prospective studies elevated cholesterol levels were associated with heightened cognitive decline or dementia risk[112]; in some even after adjusting for the effects of other vascular risk factors. However, contradictory results were obtained by other studies, where puny or no such associations were found[113,114] and no differences were detected in serum total cholesterol or hyperlipidemia between AD, VaD and dementia-free subjects[115]. Also, in a large population based study, most participants presented progressive decrease in total serum cholesterol over a 21 year time period but moderate decrease from midlife to late life was found to add up in the risk of having a more impaired late-life cognitive profile[116]. Importantly this finding remained significant after adjusting for confounders such as sociodemographic variables, APOE ε4 genotype, history of cardio/cerebrovascular conditions, and lipid-lowering treatment[116]. Additionally, increased total cholesterol measurements at ages 70, 75, 79 were positively associated with preserved cognitive capacity over the following decade in a community dwelling elderly cohort[117]. Therefore, it has been suggested that it is midlife elevated total cholesterol that threatens cognition in late life, whereas late onset elevated cholesterol in the elderly may play a protective role for brain health[118,119]. Literature on statins and their impact on cognition has also provided conflicting results. Several reports of

adverse effects, primarily communicated by observational studies, contradict the majority of randomized controlled studies, were statins had either a neutral or a beneficial cognitive effect[120]. Therefore, given the vascular benefits of their use, suspicion of secondary cognitive impairments should not lead to their discontinuation, rather to a switch to a less lipophilic form of statin, which may prevent crossing of the blood-brain-barrier (BBB) and reduce possible cognitive complications[121].

Hypertension: Obesity causes blood pressure (BP) elevation, a key vascular risk factor with well-established adverse effects on cognition. In a series of longitudinal studies midlife hypertension (around age 50) has been associated with increased cognitive decline 20 to 25 years later. For instance, in the Framingham[122] and Killander et al.'s study[123] midlife initial BP measurements, especially among individuals not receiving antihypertensive treatment, were found to negatively correlate with cognitive capacity after 12-14 and 20 years, respectively. Moreover, examination of the BP-cognition relationship in older hypertensive patients (65 years average age) revealed a 2.8-fold greater risk of cognitive decline emergence over the much smaller monitoring period of 4 years[124]. MCI status in later life was not significantly associated with middle age raised systolic BP by its own virtue, but when combined with high total cholesterol the risk of MCI emergence was doubled[125]. Dementia, either AD or VAD has also been recognized as a highly probable outcome of long-standing elevated BP[126]. In a retrospective study, dementia risk after 30 years was estimated at 24%, with entry age of hypertensive participants at 40 to 44 years[127]. However, just like the obesity-cognition association, the relation between hypertension and cognition is not a linear one, given for instance that BP may drop when AD develops[128] and this decline depends on dementia severity[129] .

Obstructive Sleep Apnea: Combined with excessive daytime sleepiness, OSA patients frequently complain for reduced alertness, short-term memory problems and lack of concentration[130]. Indeed, chronic sleep fragmentation and intermittent hypoxemia due to nocturnal shallow or paused breathing, have been associated with impairments in attention, episodic memory, working memory as well as executive functions[131]. When compared to healthy controls, OSA subjects exhibit lower scores on digit backward tests[132] and other working memory measures[133], more lapses and longer reaction times on attention/vigilance tasks[134–136] and tests of inhibition[132], increased number of impaired decisions [137], more steps and time needed for solving problems[132], as well as reduced mental flexibility and fine visual-motor coordination[132,138–140]. Language is much less commonly and severely affected[134,140–142]. Implementation of continuous positive airway pressure (CPAP) as a treatment method significantly improves attention, vigilance and memory problems[143], though executive difficulties improve only to a small or moderate degree[142] and negative findings on psychomotor speed and fine coordination do not seem to be attenuated[144]. However, even in cognitive domains where significant improvement is observed, studies have shown that complete normalization of performance is not achieved[138,141,145], suggesting that OSA, mostly as a result of repetitive hypoxemia, may permanently disrupt the endothelial and neuronal integrity of the brain areas[146] associated with the aforementioned functions.

To conclude, there is strong evidence that medical conditions resulting from excess body weight are associated with increased risk of cognitive decline and dementia. However, their co-occurrence, shared consequences (e.g. atherosclerosis) and interactions with normal aging processes, which still remain the primary risk factor for cognitive degradation, obscures efforts of distinguishing their independent impact on brain health. Some reviews report an approximately 1.5 risk of dementia for each of these factors[147], while others

conclude that diabetes and hypertension are more clearly related to poor cognitive outcomes with moderate effect sizes for all risk factors[148]. Moreover, research on reduction of cognitive decline and dementia risk through drugs used on vascular risk factors treatment has not given conclusive answers yet[149].

Evidence of cognitive impairment independently of obesity medical consequences

In the early stages of research on obesity, adipose tissue was viewed solely as an energy store and high-profile findings regarding the relationship between cognitive decline and CVD risk factors undermined notions that obesity affects health directly. Instead, the predominant idea was that obesity merely predisposes for or aggravates the effects of diabetes, hypertension, high cholesterol, OSA and other obesity associated health risk factors (e.g. smoking)[150]. However, recently accumulating evidence suggests that the poor performance of obese individuals on neuropsychological tests may occur irrespectively of those physiological consequences[151]. Studies, adjusting for metabolic, vascular risk factors and other neurocompromising variables have contributed significantly to this direction, revealing obesity-related impairments in several cognitive domains.

Memory and learning functions were naturally at the center of interest. For instance, episodic and semantic memory were accessed in a large, population based, cross-sectional study[152] which recruited middle aged (35–55 years), "young-old" (60-70 years) and "old-old" (75-90 years) normal-weight and overweight participants (BMI ≥ 25 or WHR> 1.0 for men and 0.8 for women). Patients with dementia, diabetes and hypertension were excluded in secondary analyses in order to compare the effect of obesity with and without those confounders. Overweight persons scored lower on episodic memory tasks in relation to their normal-weight peers, but this difference was attenuated after controlling for hypertension.

In contrast, similar findings on semantic memory remained significant, across all age groups even after adjustments. Verbal list-learning capacity was examined cross-sectionally in a large sample (aged 21 to 82 years), rigorously screened for medical conditions known to affect cognitive function (i.e., cardiovascular disease, diabetes, neurological disorders and head injury). Both immediate and delayed recall and recognition was found to be impaired among obese participants. Notably, the magnitude of these differences did not appear to vary with age. Similar results were found in another prospective large-scale study of 2.223 apparently healthy men and women (aged 36 to 62 years at the time) tested twice over a 5 year period[153]. Controlling for sex, educational level, blood pressure, diabetes and certain psychosocial variables, analyses revealed that higher initial BMI was associated with lower memory performance at baseline and greater decline (number of words recalled) at follow up. Over time BMI changes were not associated with cognitive fluctuation.

Apart from verbal, visual memory abilities were also examined in relation to different obesity indices (BMI, WHR, WaistC) making use of data coming from the Baltimore Longitudinal Study of Aging[154]. Cross-sectional results showed that in this cohort of community dwelling volunteers (average age 55.5 years, range 19-93 years), BMI and WaistC were associated with lower performance on one of the two verbal memory tests utilized, while BMI and WHR were negatively associated with scores on the visual retention test. Longitudinally, accumulating obesity expressed in either of the tree indices, was found to impact visual memory resulting in cognitive deterioration over time. Again, researchers controlled for confounders such as age, sex, years of education, hypertension status, glucose intolerance or diabetes status, and anti-lipid medication use.

Further cognitive domains were assessed in the same study[154], including *language*. Whereas confrontational naming ability (accessed via the Boston Naming test) was not

associated with any obesity index, both semantic and phonemic verbal fluency (the examiner requests words starting from a specific word or category) was lower for subjects with wider WaistC and bigger WHR, respectively. It should be noted, however, that verbal fluency is thought to measure executive abilities as well (strategic retrieval from semantic memory) therefore this finding is difficult to interpret as reflecting language impairment per se.

Gunstad et al.[154] employed the Trail Making Test Part B, a frequently used *executive test* of shifting and mental flexibility, but failed to find associations with obesity indices at baseline. There was, however, a stronger age-related decline in performance among participants with higher WHR. Performance on Part A of the same test, an index of *visuospatial coordination*, as well as on a mental rotation test, followed almost the opposite pattern, with better scores achieved both at initial and final measurement when WHR and BMI were elevated. Executive decrements in particular were also the main finding in a sample of extremely obese individuals (BMI≥40), who underwent neuropsychological assessment with a wide range of tests, covering nearly all cognitive domains, as part of a bariatric presurgical protocol. Differences between individuals with and without the medical co-morbidities of hypertension, type II diabetes and obstructive sleep apnea in this clinical sample failed to reach significance[155]. Likewise, an extensive neuropsychological battery was employed in a cross-sectional design of persons undergoing abdominal obesity[156]. The detected difficulties in scanning, tracking and abstract reasoning, all aspects of executive function, were inversely related to WaistC and remained significant after adjusting for all covariates (age, education, gender, examinations, smoking, cholesterol, prevalent CVD, CRP, systolic blood pressure, depression, glucose) except physical activity.

Further evidence that the performance differences found in overweight and obese adults compared to normal-weight peers may be restricted to executive tasks after controlling for potential confounding factors, emerged from a cross-sectional study of 408 healthy individuals (aged 20-82 years)[157]. Participants were free from medical comorbidities (e.g. hypertension, diabetes, CVD, thyroid disease, or sleep apnea), neurological disorders and traumatic brain injury, and other medical conditions (significant substance use, psychiatric and history of family psychiatric disorder like ADHD, schizophrenia, bipolar disorder, or genetic disorder). Adverse neurocognitive outcome was related to BMI on all cognitive tests but remained significant after controlling for comorbidities only for executive functions tests. Interactions between BMI and age were not found. Indeed, the risk of poor executive cognitive function has been found in another study[158] to be four times higher in obese compared to non-obese participants, independently of their demographic and medical characteristics.

Decision making, another facet of higher-order cognitive functions, has also been tested in obese populations. Overweight and obese women demonstrated lower resilience to immediate rewards at the expense of greater, delayed profits on the Iowa Gambling test when compared to normal-weight participants[159]. Severely obese subjects (BMI>34) from another study also failed to learn how to maximize long-term advantageous choices compared to normal-weight participants matched on age, education and Intelligence Quotient (IQ)[160].

Nonetheless, two studies have reported null or negative results. Ward et al.[161] assessed episodic learning, working memory and processing speed in 108 participants (44-66 years old). None of those domains was found to be associated with high BMI per se and only episodic memory correlated negatively with diastolic BP. It should be noted though that the

scarcity of results may have been due to low number of obese individuals (n=21) in this sample. In another prospective study the focus of interest was changes in adiposity and cognitive function. Data from community dwelling middle-age and older women (average age 58.72 years) showed that weight changes in either direction predicted poor visual memory.

In summary, there is considerable, yet not conclusive, evidence that excess adiposity in middle age is associated with subclinical cognitive impairment (in addition to prospective increased risk of dementia). Impairments have been detected in memory and attention, but executive functioning may be preferentially affected in this population, with obese individuals exhibiting increased impulsivity, reduced cognitive flexibility, and poorer organizational and planning abilities. Importantly, these associations remain significant after controlling for key medical variables, such as CVD risk factors, which are well known to directly affect cognition adversely. This suggests that contrary to earlier belief, the neurocognitive sequelae of obesity might be established much prior to the onset of overt obesity medical comorbidities. Additionally, obesity appears to predict cognitive decline but changes in weight itself do not consistently predict changes in cognition. These results highlight the need to identify more direct and proximal risk factors linking cognition to adiposity.

1.3 Chronic Low Grade Inflammation

Global rise of overweight and obesity, as well as the ensuing tide of their adverse medical consequences, have brought the structural and functional characteristics of adipose tissue into the research spotlight. Indeed, surmounting the previous view of adipocytes as merely a passive depot for energy storage, there has been a rapid acceleration in our knowledge relative to adipose tissue's major role as a highly active endocrine organ[162]. Adipose tissue seems to contribute to obesity-induced pathologies partially via altered immune responses, similar to those seen in infection and autoimmune disease[163].

From typical inflammation to metaflammation

Inflammation as a primary response of innate immunity at the presence of a threatening stimulus (infection or trauma) forms the first line of an organism's inner defense and a pivotal life-sustaining mechanism[164]. *Acute inflammation*, the typical inflammatory response, is a short-term process of rapid onset, principally driven by activation of macrophage cells[165]. Initiation of this process lies in the detection of a harmful protein (bacterial or fungal) by the specific ligands of the Toll-like receptors (TLRs) located on the surface of the macrophages. Among this receptors family, Toll-like receptor 4 (TLR4) is the best described and in the presence of ligand lipopolyscharide (LPS), initiates a signaling cascade leading to the nuclear traslocation of the transcriptional nuclear factor κB (NF-κB) within the macrophage. A swift first surge of pro-inflammatory cytokines (IL-6, TNF-α, IL-1) is secreted, while a second slower surge of anti-inflammatory factors (IL-10), reactive oxygen species and cell adhesion molecules follows. Early cytokines favor blood clotting processes and switch hepatic protein synthesis to acute-phase proteins (CRP, serum amyloid A [SAA]

and serum amyloid P) which are necessary for homeostasis rebound after injury[166] Chemokines on the other hand, such as IL-8, attract leukocytes to the site of injury or infection[167]. Finally, late-response anti-inflammatory cytokines such as the IL-10, contain the inflammatory response, allowing the return of circulating inflammatory cytokines to normal levels[165].

Therefore, a vital element of this defense mechanism is not only its rapid and effective mobilization but also the rapid and effective resolution of induced inflammation[165]. Failure of this process to terminate leads to persistent presence of subclinically elevated levels of inflammatory factors (levels higher than baseline, but many-fold lower than those found in acute inflammation), a state termed *chronic inflammation*, resulting in the long term into tissue destruction, fibrosis and necrosis[168]. When inflammatory factors persist beyond the limits of the injured or diseased tissue, involving the endothelium and through that other organ systems, chronic inflammation becomes *systemic*.

Obesity is associated with systemic, chronic low grade inflammation (CLGI). Hotamisligil et al.[169] were the first to show the existence of significantly more TNF-a mRNA in the adipose tissue of obese mice compared to lean littermates. Confirmation of this finding in humans soon followed[170] and today CLGI in obese individuals has been well documented on the basis of subtly elevated circulating levels of cytokines and acute-phase reactants, such as IL-6, IL-8, IL-18, TNF-α, CRP, insulin, blood glucose, and leptin[171–175].

In fact, it is now generally accepted that CLGI is the first and foremost physiological consequence of obesity and a vast literature has targeted the pathophysiological mechanisms that give rise to this process, as well as the pathways linking CLGI to insulin resistance and vascular endothelium deterioration. The importance of CLGI in obesity-related pathogenesis and progression, renders it as an important candidate for therapeutic

interventions and has enhanced the understanding of CLGI as a pathophysiological entity per se, hence justifying the coinage of a new term: metaflammation[176]. Even though the liver contributes to metaflammation development, in contrast to the typical inflammatory response, the key organ in this process is adipose tissue.

Obesity, adipose tissue and Chronic Low Grade Inflammation development

Adipose tissue consists predominantly of adipocytes, but other cell types such as pre-adipocytes, histiocytes, fibroblasts, vascular endothelial cells, T-regulatory lymphocytes and macrophages are also vital functional elements. As mentioned above, adipose tissue secretes a large number of bioactive substances including hormones, immune mediators, growth factors and chemoattractant proteins[177], through which it interacts with both innate and adaptive immunity. The highly "immune" profile of a primarily metabolic tissue, can be justified by its close evolutionary affinity with the immune system[178]. Extensive communication of the two is crucial for the survival of the organism, as efficient allocation and usage of energy reserves is better facilitated by such an interaction, while neutralization of invading pathogens requires increased energy investment and subsequently efficacious insulin signaling[179]. In higher organisms this is illustrated in the shared characteristics between adipocytes, immune and liver cells with the common expression of TLRs on their membranes, the activation of essentially the same signaling pathways and their analogous structure (adipocytes are linked to macrophages in adipose tissue and hepatocytes to Kupffer cells in the liver)[179].

Adipose tissue is typically classified into two forms: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT, which is located both subcutaneously and within the trunk, is the primarily storage deposit of energy in the form of triglycerides and the starting

point of lipid mobilization for systemic use by other tissues requiring energy[180]. BAT on the other hand, is believed to produce heat (nonshivering thermogenesis) through oxidative phosphorylation[181].

Obesity entails primarily accumulation of lipids in the white adipocytes due to either sustained overnutrition and/or low energy expenditure from physical inactivity. Their ability to remarkably vary their diameter to accommodate excess lipids (10-15fold)[182] though functional is not unlimited. Gradual overexpansion of the adipocytes is believed to be the primary cause of CLGI development[183,184] through various mechanisms, evident mainly by the large infiltrating number of macrophages in this tissue. Their accumulation has been found to be proportional to the degree of adiposity both in rodents[185] and humans[186]. The most important mechanisms of CLGI emergence seem to be:

Local tissue hypoxia: Disproportionate growth of adipose tissue not only results in increased oxygen demand, which by far exceeds the delivery capacity of the resident vasculature[187], but also mechanically leads to capillary rarefunction[188,189], further reducing oxygen supply and nutrient delivery. Conjointly, both processes contribute to an ischemia-induced adipocyte necrosis and the commencement of the inflammatory response with macrophage infiltration. Additionally, as will be described below, the poor anti-inflammatory character of adipose tissue in the obese (featuring among others reduced amounts of adiponectin) fails to pacify the irritated vascular endothelium. In parallel the strong pro-inflammatory properties of this tissue boosts activation of the endothelial cells which in turn express adhesion molecules and chemotactic factors that speed up and intensify the local inflammation procedure[190].

Phenotypic alteration of the obese adipose tissue: Enlargement of the adipocytes promotes the conversion of adipose tissue into a metabolically dysfunctional phenotype

with activation of the TLR4-NFκB pro-inflammatory cytokine cascade in both enlarged adipocytes and resident macrophages. Two model pathways have been suggested: the first postulates that hyperplastic adipocytes release more free fatty acids which prompt the expression of TNF-α from nearby macrophages. In turn TNF-α initiates the production of chemoattractant proteins (such as monocyte chemoattractant protein-1 [MCP-1] or C-C motif chemokine ligand-2 [CCL2]) by the adipocytes[191]. Subsequently, transendotheliac macrophage migration is enhanced and the characteristic crown-like structures are formed, with macrophage accumulation around apoptotic adipocytes in inflamed adipose tissue[192,193]. Importantly, apart from the quantitative there is also a qualitative switch in the macrophages of the obese microenviroment: instead of macrophages expressing anti-inflammatory markers of an M2 or alternatively activated state (as seen in the lean adipose tissue), obese macrophages express the pro-inflammatory M1 type or classically activated macrophages[194]. Whereas M2 cells primarily secrete interleukin (IL)-10 and IL-1ra and their action is associated with the repair of injured tissue and promotion of inflammation resolution[195], M1 cells secrete TNF-α, IL-1 and IL-6 and are believed to promote insulin resistance[196]. The latter pathway may involve obesity related blockage of the STAMP2 (six-transmembrane protein of prostate)[197], a membrane receptor expressed in lean adipocytes that normally inhibits the TLR4 and associated cytokine receptor cascade[198].

Increased apoptosis of the enlarged adipocytes: Adipocytes that undergo hypertrophy due to triglyceride overload are led to apoptosis, thus augmenting the inflammatory reaction within the obese adipose tissue[199]. Location of the adipocytes is important, with truncal cells being less resilient to enlargement than subcutaneous adipocytes, which undergo apoptosis at a much greater size[200]. The latter are also more likely to maintain their anti-inflammatory properties when enlarged[201].

Changes in the brown/white adipocyte ratio: It has been shown that CLGI development is promoted further when the ratio of white/brown adipocytes increases[180].

Taking in consideration the above mechanisms, current understanding of the adiposity-induced metabolic dysfunction postulates that this is partly due to an imbalance in the expression of pro-inflammatory and anti-inflammatory adipokines[163], contributing to the pathogenesis of the medical conditions frequently comorbid to obesity[202,203]. Markedly, adiponectin production, the most abundant anti-inflammatory and insulin sensitizing adipokine expressed from the white adipose tissue of lean subjects, is downregulated in obesity[204,205]. Its lower circulating levels, which are strongly and negatively associated with anthropometric indices of adiposity and fat accumulation, are believed to play a key mediating role in the CLGI development by further activating both innate and adaptive inflammatory mechanisms, resulting in insulin resistance and the development of a full-blown metabolic syndrome[206]. CLGI is now a well-established causal factor of insulin resistance and T2DM[207], with increased levels of the inflammatory marker CRP (which are consistently detected at elevated levels in the blood stream of obese individuals[208]) and its inducer IL-6 being predictive of the development of T2DM in a range of populations[209]. The involvement of CLGI in the pathogenesis of atherosclerosis has also been confirmed[210]. Additionally, the observed strong link between inflammation and other obesity-related conditions, such as hypertension[211], dyslipidaemia[212], NAFLD[213] and OSA[214] are further examined and the underlying CLGI-inducing mechanisms are being increasingly clarified. There is also accumulating evidence of reduced obesity comorbidities via inflammation modulation through diet[215] or bariatric surgery[216] weight loss, exercise[217] and replacement of saturated fat consumption with omega-3 fatty acids[218]. Such findings promote a new perspective in understanding these classic therapeutic strategies and investigation of the

effectiveness of other intervention methods such as use of PPAR ligands[219,220] and statins[221,222].

Inflammation and cognition

Data from several sources implicate CLGI in cognitive impairment. Inflammation has been found to play a central role in different types of dementia, particularly in AD, in the pathological mechanisms of which involvement of inflammatory markers IL-1, IL-6, CRP and TNF-α has been clearly demonstrated[223,224]. Postmortem autopsy in late-stage AD individuals has revealed increased and relatively selective concentration of several different inflammatory factors, such as proinflammatory cytokines, acute phase proteins, complement factors and activated microglia in the characteristic AD beta-amyloid plaques and neurofibrillary tangles[225]. A genetic component in the involvement of inflammatory factors is further suggested by associations between presence of related polymorphisms and AD occurrence risk[226]. Moreover, there are indications that this risk may be lessened by use of nonsteroidal anti-inflammatory drugs (NSAID)[227]. Likewise, VaD is also affected by inflammatory factors such as TNF-α and cytokines[228].

Although there is still no conclusive evidence as to whether inflammatory processes precede or follow dementia-related brain lesions, there are findings consistent with the notion that inflammation predisposes and/or exacerbates cognitive pathologies. For example, an inflammatory upsurge is often observed before clinical onset of AD or VaD dementia[229] but even more importantly, measurements of elevated inflammatory markers have been associated with future dementia emergence decades before actual diagnosis. In the Honolulu-Asia Aging study, a large scale study of 1050 Japanese men tested at baseline at an average of 55 years and followed for up to 25 years, revealed that participants initially

classified in the upper three quartiles of CRP concentrations were at a tree-fold raised risk for dementia development (AD and VaD combined) compared to those in the lowest quartile, independently of cardiovascular disorders[230]. Interestingly, acute systemic inflammation seems to enhance dementia advancement too, as shown in a study of 300 community-dwelling AD patients of various severity, whose upregulation of TNF-α serum levels as a result of acute inflammatory events was followed by a two-fold increase in the rate of cognitive deterioration over the next six months[231].

Moreover, amelioration of CLGI has also been linked to milder patterns of cognitive impairment detected in non-demented elderly populations both cross-sectionally and longitudinally. Ravaglia et al.[232] using the Mini-Mental State Examination (MMSE; a commonly used dementia screen test which provides a crude assessment of general cognitive ability), found a statistically significant inverse association between performance on this test and CRP concentrations in a cross-sectional examination of 540 relatively healthy elderly people (mean age 73 years). Usage of the modified MMSE gave analogous results in another cohort of 3014 elders (mean age 74 years), with those suffering from metabolic syndrome and belonging in the highest CRP tertile at enrollment, presenting greater cognitive 4-year decline compared to those with metabolic syndrome and low inflammation[233]. Data from two independent, population-based cohort studies with 4- to 5-year follow up periods (n=3874 averaging 72 years in the Rotterdam and n=491 85-year olds in the Leiden 85+ study) showed that higher levels of IL-6 and CRP were cross-sectionally associated with lower scores on tests of global and executive function tests, whereas a steeper annual decline in memory was linked only to IL-6 levels[234]. Baseline measurements of CRP in a much smaller sample of 65 ostensibly healthy elder individuals (mean age 54 years) were also inversely related to delayed verbal memory performance 6 years later[235].

Apart from the clinical end point of dementia or mild cognitive decline in well-functioning elders, where attribution of causative characteristics in inflammatory processes is difficult due to often concomitant and even serious age-related disease conditions, similar findings in younger ages, potentially less affected by such factors, are of great interest. The relationship between midlife inflammation levels and cognitive performance was examined cross-sectionally by Marsland et al.[236] who administrated a battery of neuropsychological test to 504 healthy adults (aged 30 to 54) and inversely associated their performance on auditory recognition, working memory, and executive function with peripheral levels of IL-6, independently of age, gender, race, education, BMI, smoking or hypertension. Very recent analysis from the ongoing Whitehall II cohort study[237] addressed the same question longitudinally. Initial results showed that peripheral inflammatory levels of IL-6 and CRP in mid-life (i.e., between 45 and 69 years) emerged as prognostic markers of future cognitive decay within a 10 year timeframe (not just dementia occurrence as documented in the Asia-Honolulu study[230]). Results were also adjusted for a wide range of possible confounders. Participants with high IL-6 (regardless of CRP levels) scored lower on reasoning ability tests compared to their low IL-6 peers cross-sectionally and were also more likely to experience more rapid cognitive decline in this domain, as well as 1.81-fold receding global cognitive ability (measured by MMSE).

Vitally, regarding normal cognitive ability, erythrocyte sedimentation rate (ESR), a non-specific marker of CLGI was linked to reduced performance on a IQ test in healthy young adults aged 18-20 years (n=49321). This relationship persisted even after adjustment for several confounders, such as cardiovascular risk factors or childhood circumstances, and was only slightly attenuated by childhood socioeconomic position (SEP)[238]. Collectively, these

findings support the characterization of inflammation, and especially chronic inflammation exposure, as a significant culprit for gradual cognitive degradation.

3. Objectives of the study

3.1 CLGI as a potential mediating parameter of two alternative causal path models

As outlined in the introduction section, compromised neurocognitive function is associated with obesity as well as inflammation. CLGI represents the earliest consequence of obesity, preceding and precipitating well established obesity-related factors adversely impacting cognition (i.e diabetes, hypertension, high cholesterol, OSA). Taken together with the fact that cognitive impairments have been detected independently of those obesity medical consequences, CLGI emerges as a serious potential *direct* link between obesity and its neuropsychological sequelae.

According to one hypothesis, obesity leads either directly (via CLGI) or indirectly (via obesity-related comorbidities; figure 10) to disturbances in brain function manifested by lower performance on neuropsychological tests. Apart from the already presented evidence, forward causation is further supported by some indications of reversibility in the obesity-induced poor cognitive outcome through weight loss, which is known to effectively reduce levels of plasma inflammatory markers[215]. For instance, morbidly obese patients who underwent bariatric surgery, performed better at a 12 month memory follow up test, in contrast to obese control subjects, who did not receive surgery or other obesity treatment and demonstrated continuing cognitive deterioration. Patients in both groups had scored equally low at baseline assessment[239]. Another research group reported improvement in attention and memory test scores lasting for up to 24 months after bariatric surgery, while executive function recovery culminated at 36 months[240].

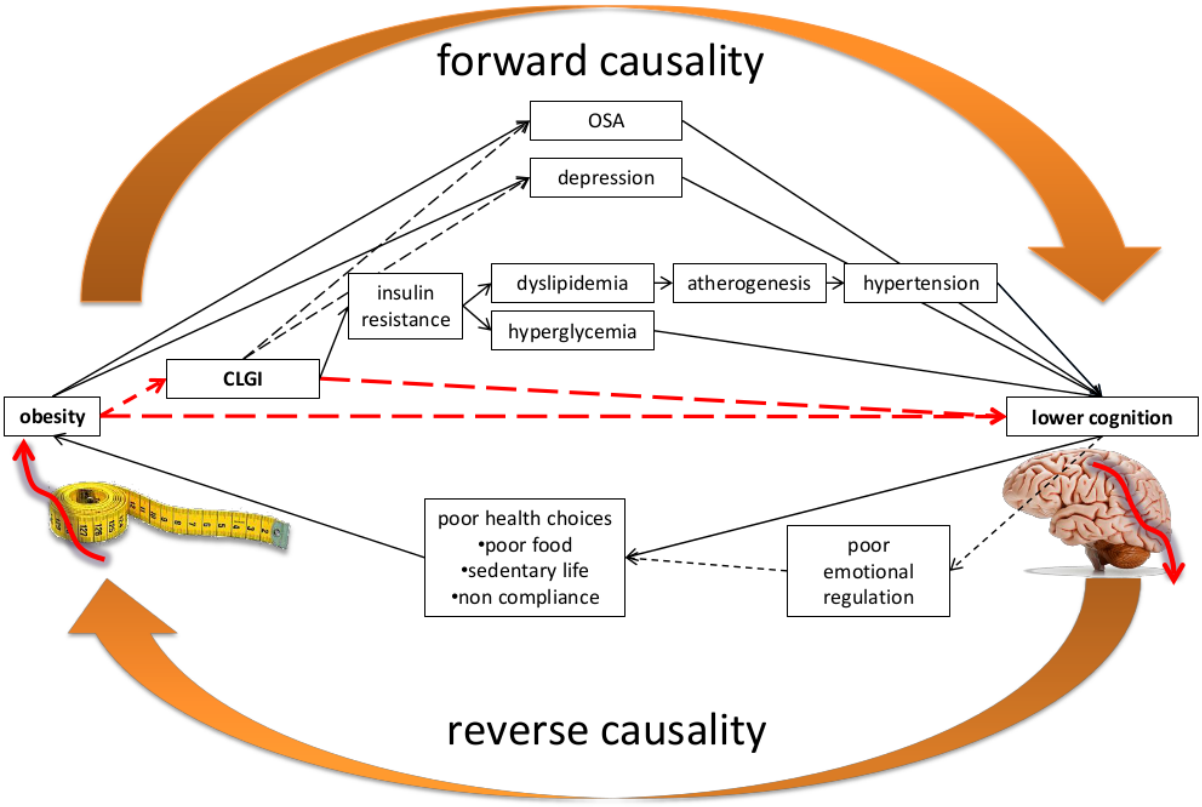

Figure 10. Two purported, alternative pathways connecting obesity and low cognitive performance**.**

On the other hand, a less intuitive alternative path model (reverse causality; 10), highlights that poor cognition and in particular executive functions (including planning, cognitive flexibility and logical reasoning ability) may explain obesity development through the adoption of poor health choices, given that these abilities are important determinants of everyday decision making (e.g. dietary behavior, low inhibition of palatable yet of low nutritional value food consumption and low physical activity) both in adults[241,242] and children[243]. A growing literature on cognitive reserve predicting either future weight gain or weight loss success is in favor of this "reverse causality" premise. In a longitudinal study, low

accomplishment of 4 year olds on executive tests predicted raised levels of adiposity after 2 years, while the opposite pattern was detected for children with higher verbal abilities at initial measurement[244]. Another study[245], followed a large birth cohort assessing fine motor coordination and hand control at age 7, 11 and finally at 33 years of age. Statistical adjustment for possible confounders (including BMI, general motor disability, and SES) did not eliminate statistical differences in final adult weight gain between children with poor motor abilities (part of the executive subdomain of psychomotor speed and coordination) and children with higher scores. Even in populations with confirmed cognitive impairments such as morbidly obese candidates for bariatric surgery[246], weight loss success and, more importantly, maintenance of reduced weight was significantly predicted by the degree of cognitive function as accessed before surgery[247–249].

Such findings come as no surprise as they corroborate much older observations of associations between IQ and future development of health problems, such as coronary heart disease, stroke[250], full blown metabolic syndrome[251], and even total mortality[252]. Notably, studies on personality traits, another factor strongly argued to contribute to such relationships, failed to detect analogous associations[253]. This is important, because personality characteristic attributions (like laziness or weakness of will[254]) are often part of the widespread social perception of obese and overweight persons, not to mention often part of their own self perceptions[255].

In conclusion, exploration of compromised cognitive function in the presence of obesity should be further addressed under the light of new endocrinological data highlighting the role of CLGI as the most likely cornerstone for all obesity related pathologies. Directionality of the obese-cognition impairment relationship is also of great interest.

3.2 Additional obesity related factors that may hamper cognitive functioning

Among mood disorders, depression in particular appears to have a major impact on body weight dysregulation and vice versa. A recent meta-analysis including more than 58700 subjects was illustrative of the bidirectional association between depression and obesity: obese persons had a 55% higher risk of developing depression over time in comparison to normal weight subjects, whereas subjects with depression had a 58% increased risk of becoming obese compared to healthy persons[256]. Compromised cognitive function, especially in the areas of sustained attention and mental flexibility has been identified as a characteristic of clinical and subclinical depression[257–259]. Moreover, elevated levels of stress and anxiety, have been linked to impaired performance on cognitive tasks[260] as well as increased body weight[261]. Thus, psychoemotional well-being, as indexed by the absence of symptoms of depression and anxiety has been implicated as a potential mediator of the obesity-cognitive association[262]. Finally, a protective role of exercise on the adverse effects of obesity on several psychological domains has been documented including that of cognition[263,264].

3.3 Objectives of the study

The current cross-sectional study examined the relation between obesity-linked immune and metabolic effects and general cognitive capacity. Using data obtained from young and middle-aged Greek volunteers who were largely free of other clinically evident obesity-related medical comorbidities, the study pursued the following specific goals:

First, we examined the possible negative association between body weight/fat content and fluid intelligence, as measured by a non-verbal logical reasoning test (fluid intelligence).

Second, we compared two alternative path models regarding the direction of the obesity-cognition association, including CLGI as a mediator variable. Importantly, we assessed the potential mediating role of CLGI by controlling for the effects of additional physiological (metabolic dysfunction indices and adiponectin), psychological (anxiety and depression symptoms), and life-style (exercise) measures.

Third, we examined whether the hypothesized mediated effects of obesity (through inflammation), may depend upon the level of psychological (depression and anxiety symptoms), life style (exercise habits), and physiological variables (HOMA-IR, adiponectin) variables.

Fourth, we addressed the question whether the purported direct and/or mediated effects of body weight/fat content on fluid intelligence were determined by the presence of clinical obesity.

4. Methods

4.1 Participants and procedures

Out of two hundred fourteen (214) subjects addressed, one hundred ninety nine participants (199) were finally recruited, through direct contact during regularly scheduled appointments for routine clinical evaluations (e.g. complete blood count or other more specific tests appropriate for their health condition) at primary care facilities (private endocrinology practice and the University Hospital outpatient clinic). Participants were free of major and chronic autoimmune or connective tissue diseases. Other existing medical comorbidities were quantified using the Charlson Comorbidity Index (CCI)[265]. Individuals with self-reported history of mental diseases, including depression symptoms, and neurological disorders or traumatic brain injury (resulting in >10 minute loss of consciousness) were excluded from further analyses (n=7). Additionally, participants with a recent history of infection (reported or diagnosed during clinical examination) or demonstrating leukocytosis (WBC > 10.000; n=12), were not included in the final sample (n=180). Obesity indices, including BMI, Waist to Hip Ratio (WHR) and body fat composition were measured on-site in a quiet examination room on a scheduled appointment. The fluid intelligence test and the self-report questionnaires were also administrated in the same appointment and a semi-structured mini interview on health related issues (e.g. smoking, alcohol consumption, past medical history) was conducted.

Participants were assigned to three groups: normal-weight (BMI range: 18.5-24.99), overweight (BMI range: 25-30) and obese (BMI ≥30). Sample demographics are presented in Table 1 of the results section.

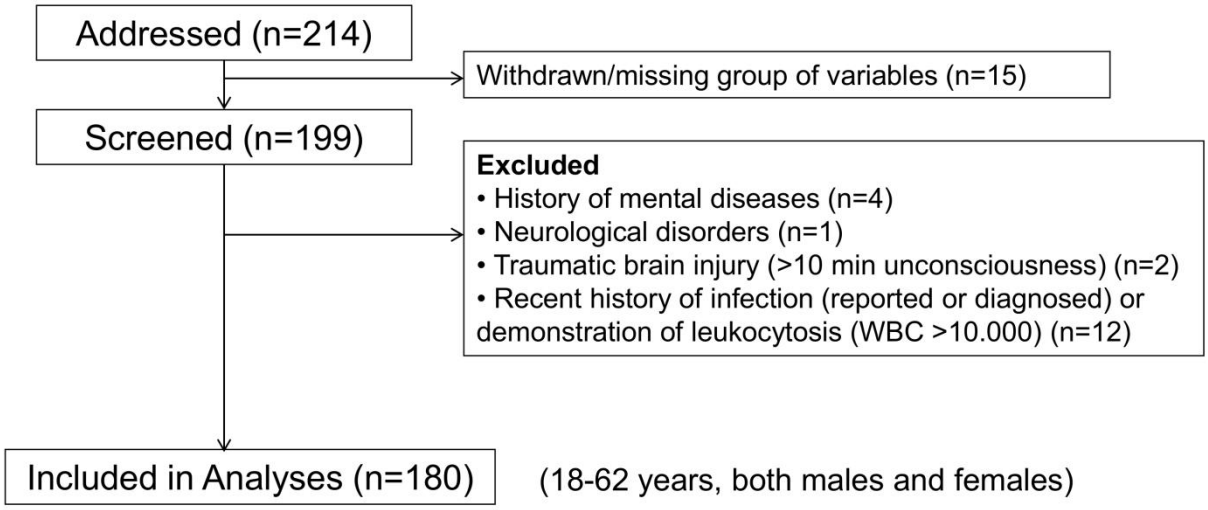

Figure 11. Flow chart of participants.

The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects had been approved by the University of Crete Hospital Ethics Committee (protocol No. 3842). All participants provided written informed consent following a detailed explanation of the protocol. Participation was voluntary and subjects were given no financial compensation for their time and effort.

4.2 Measures

Cognitive, psychological, and activity measurements. The *General Ability Measure for Adults (GAMA)*[266], is a non verbal measure of general (primarily fluid) intelligence, independent of verbal factors both in content and administration, making the test useful with diverse populations (e.g. ethnicity, language, literacy). It consists of 66 problems utilizing colored, abstract designs that require the examinee to either match a sample design (Matching scale), complete a pair of stimuli through analogy to a model pair (Analogies scale), identify logical sequences (Sequences scale) or combine pieces mentally to form a

complete geometric pattern (Construction scale). All categories were progressive, starting with relatively simple problems that then became more difficult. The correct answer is selected from a set of six choices (see Appendix part 1). Comparison data were available on 453 Greek adults (257 women and 196 men) aged 17 to 82 years (mean=39.96, SD=14.47 years) with 2-24 years of formal education (mean=13.09, SD=3.68 years), recruited from 6 broad geographical regions in the Greek mainland and islands (296 from urban and 157 individuals from rural areas or small-towns (defined as population under 10,000). The sample was divided into 9 subgroups representing full cross-over of age and education with a minimum of 30 persons per group. Education was converted into a discrete variable with three levels: 0-9 years of formal education, 10-12 years, and 13+ years. Age was also grouped into three levels (17-37, 38-50, and 51-65 years). Raw total GAMA scores were converted into Intelligence Quotient (IQ)-equivalent scores (mean=100, SD=15) adjusting for age and education level. Raw scores on each of the four GAMA subscales (matching, analogies, sequences, constructions) were converted into appropriate standard scores (mean=10, SD=3). Performance on this test is strongly correlated with scores on more comprehensive IQ measures, such as the Wechsler Adult Intelligence Scale-Revised (WAIS-R)[266]. GAMA correlated 0.74 with WAIS-R Performance Intelligence Quotient (PIQ), 0.65 with WAIS-R Verbal Intelligence Quotient (VIQ), and 0.75 with WAIS-R Full Scale Intelligence Quotient (FSIQ). The magnitude of these associations were similar in the presence of acute brain damage (r= 0.74, 0.71, 0.81, respectively)[267] and among young adults experiencing academic difficulties (r=0 .69, 0.36, 0.60, respectively)[268]. Given that GAMA was originally designed as a measure of fluid intelligence, achieving high scores on the test requires adequate engagement of functions generally considered as “executive”[269]. Such, presumed, higher order, yet diverse, cognitive functions serve the ability to coordinate goal-directed

thought and action and include complex attention, mental flexibility, inhibition, problem solving, and decision making. These functions are believed to be primarily carried out by prefrontal areas[270]. Solving the logical problems in GAMA requires successful, continuous management of working memory resources[271,272] and the ability to switch cognitive strategies in dealing with different types of alternating problems[273,274]. In fact in our Greek adult community cohort, performance on GAMA was found to correlate strongly ($r > .60$) with such measures. Internal consistency (Cronbach's $\alpha = .93$) and test-retest reliability ($r = .84$; $N = 48$) in the same cohort were adequate.

The revised edition of the *Beck Depression Inventory (BDI-II)*[275] is a 21 item self-report questionnaire, designed to access intensity of depressive symptomatology according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) in clinical and community adult samples. Each item consists of four statements arranged in order of increasing severity on a 0 to 3 scale (e.g., 0 = "I do not feel sad" to 3 = "I am so sad and unhappy that I can't stand it"). Respondents are asked to rate each set of statements according to how they have been feeling in the past two weeks, including the date of questionnaire completion. A total score below 14 points indicates minimal depression symptoms, 14 to 19 points indicate mild depression symptoms, 20 to 28 points suggest moderate depression symptoms, whereas a score between 29 and 63 points indicates severe depression symptoms. The Greek version of BDI-II[276] used in the present study has a Cronbach's $\alpha = 0.87$.

The *State – Trait Anxiety Inventory (STAI, Y form)*[277] is a self-report measure of the severity of anxiety feelings in adults. The Greek version of the *Trait Anxiety subscale (STAI-T)*[278] was used here, accessing more general and long standing anxiety. Sample items include "I feel nervous and restless", "I lack self-confidence" and reverse-scored items like "I am

content". Questions are rated on a four-point Likert scale resulting in a score range between 20 and 80 points, with higher scores indicating greater anxiety. Cronbach's α was 0.90.

Leisure-time physical activity was assessed through *Godin's* self-administered questionnaire[279]. Subjects reported the number of times spent in physical activity lasting for at least 15 min. in an average week and classified them as strenuous, moderate, or light (corresponding to 9, 5, or 3 Metabolic Equivalents [METs]). The total score was derived by multiplying the reported frequency by its corresponding MET value and summing the three products. Test-retest reliability of the total score ranged between 0.62 and 0.81[280]. As with the majority of available self-administered physical activity questionnaires, Godin scores derived from broad community samples demonstrate a somewhat inconsistent validity profile. Correlations between Godin scores and measures of energy expenditure are generally low (r = 0.10-0.32), although stronger associations with body fat have been reported[280,281]. In all analyses involving Godin data, root-square transformed scores were used to correct for significant positive skewness in the data.

Somatometrics. Total height and weight were measured to calculate BMI (kg/m^2). WHR (waist-/hip-circumference) is commonly used as a convenient index of body fat centralization (visceral obesity). Waist and hip circumference were measured at the level of umbilicus and gluteus, respectively. Total body fat percentage (BF%) was estimated through Bioelectrical Impedance Analysis (BIA) employing an Akern BIA 101, Wuerzburg, Germany. In order to further validate this technique, body fat composition was determined using the dual energy X-ray absorptiometry (DEXA) by Lunar DPX (GE Healthcare, Madison, WI) in a random subgroup of our participants (n = 23), which along with Computed Tomography (CT), is known to be the most accurate assessment methods of body fat[8]. The correlation between BIA and DEXA in this subgroup was linear and high (r = 0.91).

Biochemical indices. Morning fasting blood samples were collected in a serum-separating tube from all participants, allowed to clot at room temperature for thirty minutes, centrifuged, aliquoted, and stored at −80◦C in plastic vials for subsequent measurements. Biochemical analyses were performed at the University of Crete, Laboratory of Clinical Chemistry. Twelve participants (n=12) demonstrated leukocytosis and where excluded from further analyses. The following indices were available on all remaining 180 participants: (a) high sensitivity CRP (hs-CRP) measured by immuno-nephelometry assay on a Cobas 6000 (Roche Diagnostics International, Ltd) with a detection limit of 0.18 mg/l), (b) fibrinogen and, (c) ESR. Insulin resistance was assessed using the Homeostasis Model Assessment insulin resistance (HOMA-IR) index computed by multiplying glucose (mg/dl) by insulin (μU/ml) serum levels and dividing by 405[282]. Finally, total plasma adiponectin was assessed with the human adiponectin ELISA kit (cat.#:KHP0041; Life Technologies Corporation).

In order to simplify the set of regression and path analyses described below, we computed composite indices for somatometric (BMI, WHR, BF%), and inflammation (hs-CRP, ESR, fibrinogen) markers expressed as the mean of the respective z scores in the current sample. An exploratory factor analysis with Varimax rotation on the six measures revealed two factors with eigen values >1. Factor 1 was mainly accounted for by variance of fibrinogen, ESR, and hsCRP (factor loadings ranged between 0.68 and 0.83), whereas Factor 2 mainly reflected variance of the three somatometric measures (factor loadings ranged between 0.69 and 0.86). Cross loadings did not exceed 0.39. The correlations among somatometric indices ranged from r = 0.23 (BF%-WHR) to r = 0.81 (BMI-BF%). Correlations among inflammation indices ranged from r = 0.48 (fibrinogen with hs-CRP) to r = 0.56 (ESR with hs-CRP).

4.3 Statistical analyses

The first aim of the study was pursued through ANOVAs on GAMA standard scores with BMI group as the between subjects variable with three levels (normal-weight, overweight, obese). Physiological and clinical variables, on which the three groups should be found to vary significantly, were also entered in separate One-Way ANOVAs as covariates in SPSS v. 20.

The second aim of the study was explored through Structural Equation Modeling (SEM) comparing the two alternative, non-nested models illustrated in figure 12.

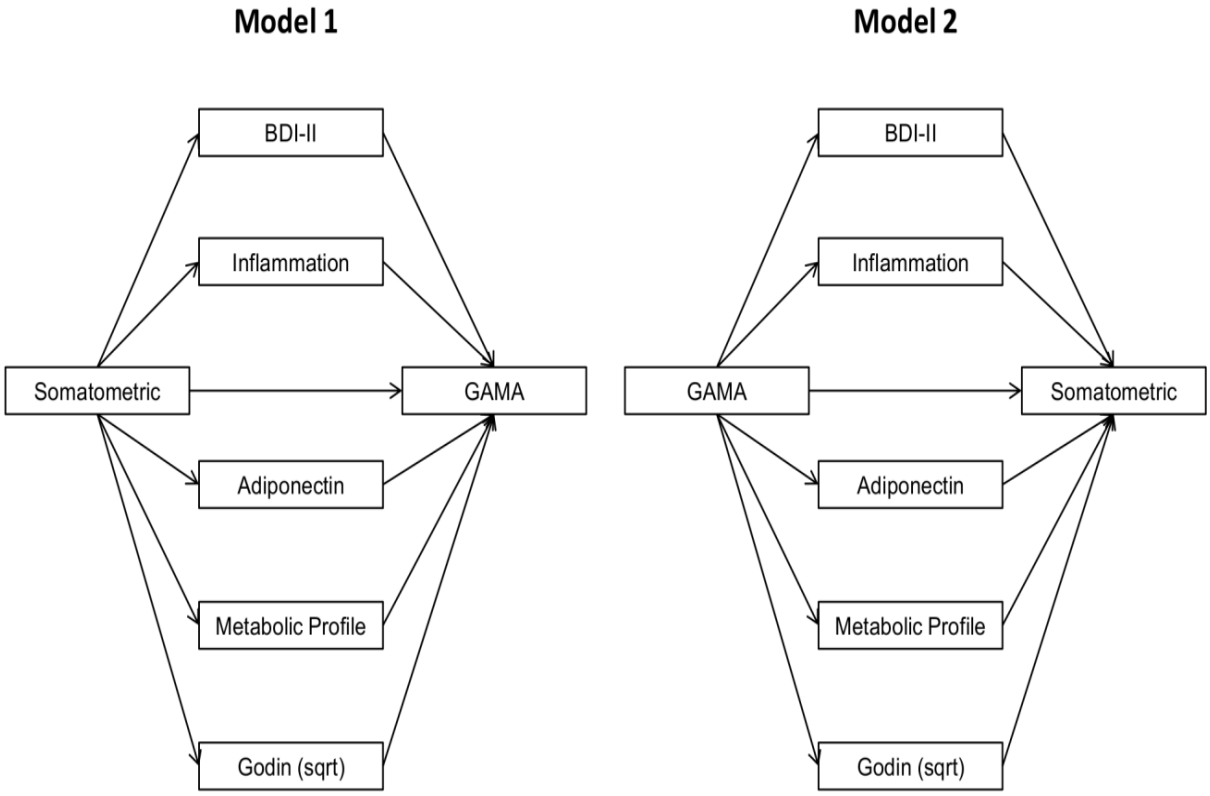

Figure 12. Two alternative models postulating an effect of obesity on cognition (model 1) or the reverse, an effect of cognition on obesity (model 2).

Model 1 postulates a direct effect of obesity (somatometric index) on cognition (GAMA total score), whereas Model 2 represents the reverse relationship. Each model

included a number of parallel mediators representing psychological (BDI-II and STAI-T scores), life-style (Godin scores), and physiological factors (HOMA-IR, adiponectin), and estimated both direct and indirect effects (i.e., through each of the mediating variables) between obesity and cognition. The two models were directly compared on fit indices calculated in Analysis of Moment Structures (AMOS; version 20; SPSS, Inc.). This statistical technique allows testing of theoretical pathways involving causal relations and thus is suitable for inferential analysis of cross-sectional data[283].

The third aim of the study was assessed through moderated regression analyses. Specifically we sought to examine if the hypothesized mediated effects of obesity (through inflammation), may depend upon the level of psychological (depression and anxiety symptoms), life style (exercise habits), and physiological variables (HOMA-IR, adiponectin) variables.

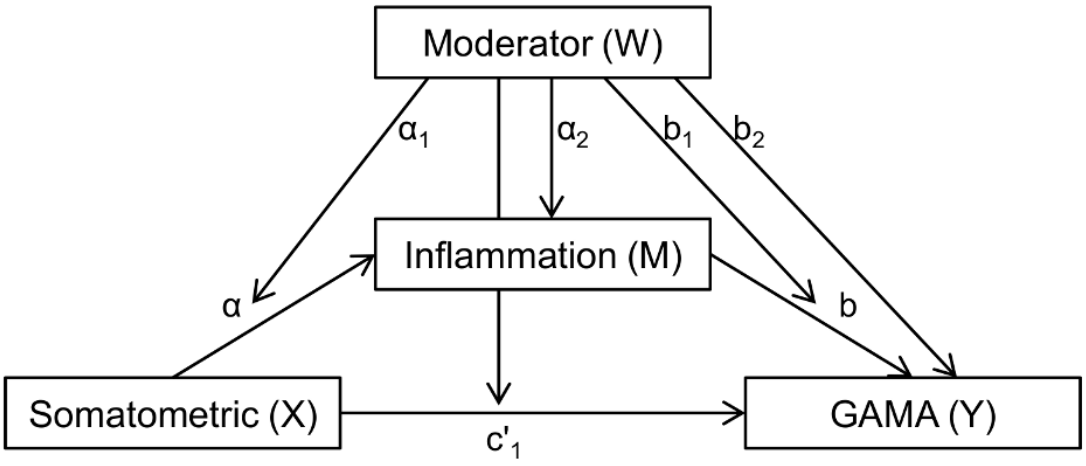

Figure 13. Schematic illustration of the proposed moderated mediation of the association between obesity and GAMA scores, which includes a residual direct effect of obesity on GAMA plus direct effects of each moderating variable on the independent, mediator, and outcome variables. The following variables were tested as moderators: obesity classification (normal weight, overweight, obese), STAI-B total score, BDI-II total score, Godin score, HOMA-IR, adiponectin.

The general model tested is illustrated in figure 13, where the mediation paths α and b linking somatometric measures and GAMA vary with each of the psychological, physiological and life-style variables. The mediator M (inflammation index) was estimated using the following equation (model 59 in Hayes[284]):

$$M = i_M + \alpha X + \alpha_2 W + \alpha_1 X*W + e_M \quad (Eq1)$$

The following equation was used to estimate GAMA scores:

$$Y = i_Y + c'_1 X + bM + b_2 W + b_1 X*W + e_Y \quad (Eq2)$$

The fourth aim of the study was pursued through moderated mediation analysis using the same model described by Equations (1) and (2) with Obesity Group as the moderator variable. Complementary, group-level analysis examined the presence of interactions between Obesity group and CLGI group (created through a median split on the Inflammation composite variable).

5. Results

5.1 BMI group comparisons

ANOVAs between-subjects confirmed the expected group differences on WHR, $F(2,177)=30.65$, $p=0.0005$, $\eta^2=0.261$, and BF% content, $F(2,177)=81.03$, $p=0.0005$, $\eta^2=0.568$. As shown in Table 1, all pair wise group differences were significant. Further tests showed that BMI groups did not differ on BDI-II, STAI-T, or Godin scores ($p>0.5$). Chi-square tests did not reveal group differences in the distribution of CCI scores, marital or financial status, or type of job.

Table 2 presents data on all inflammatory and metabolic indices for each BMI group. In addition to somatometric measurements, the three groups also differed on inflammation (ESR: $F[2,177]=14.53$, $p=0.0005$, $\eta^2=0.115$; hs-CRP: $F[2,177]=26.65$, $p=0.0005$, $\eta^2=0.218$; fibrinogen: $F[2,177]=6,841$, $p=0.001$, $\eta^2=0.07$), and metabolic efficiency indices (insulin: $F[2,177]=13.13$, $p=0.0005$, $\eta^2=0.135$; glucose: $F[2,177]=10,268$, $p=0.0001$, $\eta^2=0.096$; HOMA-IR: $F[2,177]=12.05$, $p=0.0005$, $\eta^2=0.137$; adiponectin: $F[2,177]=7.74$, $p=0.001$, $\eta^2=0.080$). With the exception of adiponectin, obese participants had higher indices as compared to both normal-weight and overweight individuals. As expected, the opposite pattern was noted for adiponectin. Given that the proportion of men was higher in the overweight (37%) than in the normal-weight (12%) and obese groups (15%; phi = .213, p = .013), the analyses were repeated with gender as an additional factor, failing to reveal any significant main effects or interactions ($p >.1$).

Table 1.

Clinical and demographic information for each obesity subgroup

	Normal-Weight	Overweight	Obese
N	55	54	71
Men	7	20	11
Women	48	34	60
Family Status			
Single	36	27	26
Married	16	25	41
Divorced/widowed	3	2	4
Type of Occupation			
Sedentary	30	24	33
Manual	4	8	8
Mixed	21	22	30
Reported Financial Status			
Poor	1	3	3
Average	30	26	42
Above average	24	25	26
Age (years)	39.91 (9.92) [19-54] †	36.71 (10.90) [18-64]	39.51 (11.38) [17-62] †

Education (years)	16.40 (2.79) [12-22] †	15.29 (2.60) [6-22] #	13.72 (2.91) [6-22] †#
BMI (kg/ m^2)	22.33 (1.76) [18.65-24.98]*†	27.37 (1.42) [25.04-29.86]*#	34.22 (3.79) [30.12-45.88]†#
WHR (cm/cm)	0.79 (0.07) [0.65-1.02] *†	0.88 (0.06) [0.73-0.97] *	0.89 (0.09) [0.69- 1.14] †
Total Body Fat (%)	27.73 (5.80) [16.50-40.70]†*	33.47 (6.00) [21.20-42.30]*#	41.53 (4.35) [28.50-51.52]†#
STAI-T	42.93 (7.65) [31-61]	42.39 (8.02) [30-63]	44.01 (8.91) [31-69]
BDI-II	10.35 (7.31) [0.00-27]	10.81 (8.22) [0.00-35]	12.85 (8.40) [0.00-48]
Godin	27.04 (17.99) [0.00-65.00]	21.81 (19.74) [0.00-79.00]	14.49 (13.95) [0.00-52.00]
CCI			
0	54	51	63
1	0	3	2
2	1	0	5
3	0	0	1

Mean (SD), range in brackets. BMI = Body Mass Index; WHR = Waist to Hip Ratio; BDI-II = Beck Depression Inventory II; STAI-T = Trait Anxiety Inventory; Godin = Leisure-time physical activity (total raw scores); CCI = Charlson Comorbidity Index. * Normal-Weight vs. Overweight, † Normal-Weight vs. Obese, # Overweight vs. Obese at $p < 0.01$.

Table 2

Metabolic and inflammation indices for each obesity subgroup

	Normal-Weight	Overweight	Obese
ESR (mm/hr)	9.24 (6.71)	11.88 (8.68)	20.01 (14.99)
	[1-30] †	[3-30] #	[3-91] †#
hs-CRP (mg/l)	0.85 (0.95)	1.53 (1.76)	4.66 (4.39)
	[0-4] †	[0-9] #	[0-17] †#
Fibrinogen (mg%)	262.38 (54.73)	269.34 (58.04)	304.64 (74.30)
	[151-448] †	[145-449] #	[142-626] †#
Insulin (µU/ml)	5.96 (3.56)	8.37 (3.91)	14.22 (13.69)
	[2-18] †	[3-23] #	[1- 79] †#
Glucose (mg/dl)	88.79 (5.53)	91.67 (11.59)	97.66 (12.90)
	[78-102] †	[60-150] #	[76-152] †#
HOMA-IR	1.27 (0.77)	1.97 (1.25)	3.58 (3.85)
	[0.38-4.24] †	[0.65-8.67] #	[0.27-18.83] †#
Adiponectin (mg/ml)	16.69 (6.25)	15.62 (6.36)	12.53 (5.40)
	[6.23-30.36] †	[4.41-30.27] #	[4.86-30.41] †#

Mean (SD), range in brackets. ESR = Erythrocyte Sedimentation Rate; hs-CRP = high sensitivity C-reactive protein; HOMA-IR = Homeostasis Model Assessment of Insulin Resistance. † Normal Weight vs. Obese, # Overweight vs. Obese at $p < 0.01$. * Normal-Weight vs. Overweight comparisons failed to reach significance.

Given that the three groups differed on age, $F(2,177)=5.94$, $p=0.003$, years of formal education, $F(2,177)=15.21$, $p=0.0005$, and gender distribution, group-level analyses on cognitive ability were conducted on age- and education-adjusted GAMA IQ scores and subscale standard scores. At the group level, the key finding was a main effect of BMI group, $F(2,177)=7.09$, $p=0.001$, $\eta^2=0.083$. Planned pair wise comparisons revealed that the obese group scored significantly lower than both the normal-weight (Bonferroni-corrected, $p=0.001$) and overweight groups ($p=0.029$), which did not differ from each other ($p>0.7$). Main group effects were also significant for each of the four GAMA subscales ($p <0.001$) and pair wise tests revealed a similar pattern of group differences (see Table 3). Importantly, group differences on GAMA IQ scores remained significant after controlling for STAI, BDI, Godin, and CCI scores, as they did after controlling for metabolic function (insulin, HOMA-IR, adiponectin). However, controlling for individual variability on the systemic inflammation composite, group differences on GAMA were all but eliminated ($p>0.24$). Results were essentially identical when ANCOVAs were performed on GAMA total raw scores controlling for participant age and education. Neither the main effect of gender or the Group by Gender interaction approached significance ($p > .8$). Power analyses indicated that for the effect size of group differences observed in the study, estimated power for detecting significant Group main effects ranged between 0.96 and 0.99 at alpha = 0.05 and between 0.84 and 0.99 at alpha = 0.001.

Percentages of individuals with “normal-range” IQ estimated were: 90%, 88%, 78% for normal-weight, overweight, and obese, respectively. The remaining participants had estimated IQ scores in the 70-85 point “borderline” range.

Table 3.

Average GAMA total IQ-equivalent scores and subscale standard scores (SD in parentheses) for each obesity subgroup

	Normal-Weight	Overweight	Obese
GAMA	104.38 (15.11) ‡	101.85 (13.77) +	94.91 (15.15) ‡+
Matching	11.19 (2.74) ‡	10.70 (2.58) §	8.56 (2.89) ‡§
Analogies	11.19 (2.67) ‡	10.88 (2.71) §	8.46 (2.78) ‡§
Sequences	10.97 (2.67) ‡	10.82 (2.54) §	8.67 (3.07) ‡§
Construction	11.06 (3.11) ‡	10.24 (2.77)	8.91 (2.75) ‡

GAMA = General Ability Measure for Adults; Bonferroni-corrected + $p < 0.03$, § $p < 0.01$, ‡ $p < 0.001$.

5.2 The role of low-grade systemic inflammation

Table 4 reveals a largely expected pattern of intercorrelations between the somatometric, inflammation, and cognitive indices (GAMA raw score). Correlation coefficients were in the moderate range meeting the essential requirement in order to further assess direct and indirect effects of obesity on GAMA (and the reverse) through inflammation.

Table 4.

Pearson correlations between variables examined in SEM analyses

	1	2	3	4	5	6	7	8	9
1. Age									
2. Education	-0.08								
3. Somatometric	0.28**	-0.32**							
4. Inflammation	0.08	-0.30**	0.47**						
5. GAMA	-0.23**	0.53**	-0.29**	-0.39**					
6. HOMA-IR	0.05	-0.16*	0.38**	0.26**	-0.06				
7. Adiponectin	0.08	0.20**	-0.24**	-0.13	0.002	-0.28**			
8. Godin	-0.25*	0.14	0.33*	0.22**	0.13	-0.19*	0.02		
9. STAI-T	-0.18*	-0.04	0.09	0.09	-0.11	0.04	-0.06	0.16	
10. BDI-II	-0.20**	-0.09	0.12	0.08	-0.21**	0.007	-0.03	0.17	0.78**

Somatometric = composite index BMI, WHR, BF%; Inflammation = composite index hs-CRP, ESR, fibrinogen; GAMA = General Ability Measure for Adults (raw score); HOMA-IR = Homeostasis Model Assessment of Insulin Resistance; Godin = Leisure-time physical activity; STAI-T = Trait Anxiety Inventory; BDI-II = Beck Depression Inventory II; *p < 0.05. ** p < 0.01.

As illustrated in Figure 14, results suggested that Model 1, which tested the hypothesis that obesity (somatometric index) impacts cognitive ability (GAMA) through inflammation, controlling for psychological, life style, and physiological processes, fitted the current data significantly better (χ^2=9.6, df=10, p=0.48, Normed Fit Index [NFI]=0.953, Comparative Fit Index [CFI]=1.00, Root Mean Square Error of Approximation [RMSEA]=0.0001) than the poorly fitting alternative Model 2 (χ^2= 34.51, df=10, p=0.001, NFI=0.830, CFI=0.866, RMSEA=0.114). Model 2 examined the reverse hypothesis that lower cognitive abilities would lead to higher rates of obesity (again controlling for psychological, life style, and other physiological processes). Finally, Akaike's Information Criterion (AIC), which is widely used to compare non-nested models originating from the same data, was considerably smaller (AIC=59.61) for Model 1 than Model 2 (AIC=84.10), suggesting better fit of the former. Notably, the smaller R^2 values in Model 1 (describing the regression of GAMA on each of the mediators) as compared to Model 2 (describing the regression of the Somatometric index on the same mediators) is explained by the stronger direct paths of each physiological/exercise variable with the Somatometric variable. It is further expected that these associations will be stronger than the direct effects of the same physiological/exercise variables on the (conceptually more distal) cognitive measure.

In order to ensure that the data set possessed adequate power for model testing, the structural model in which GAMA was a function of BDI, inflammation, adiponectin, metabolic profile, and Godin and all being a function of somatometrics was simulated with between-construct paths equal to .25, to be on the conservative side. Using a Monte Carlo simulation with 500 replications and sample sizes equal to 180 participants results pointed

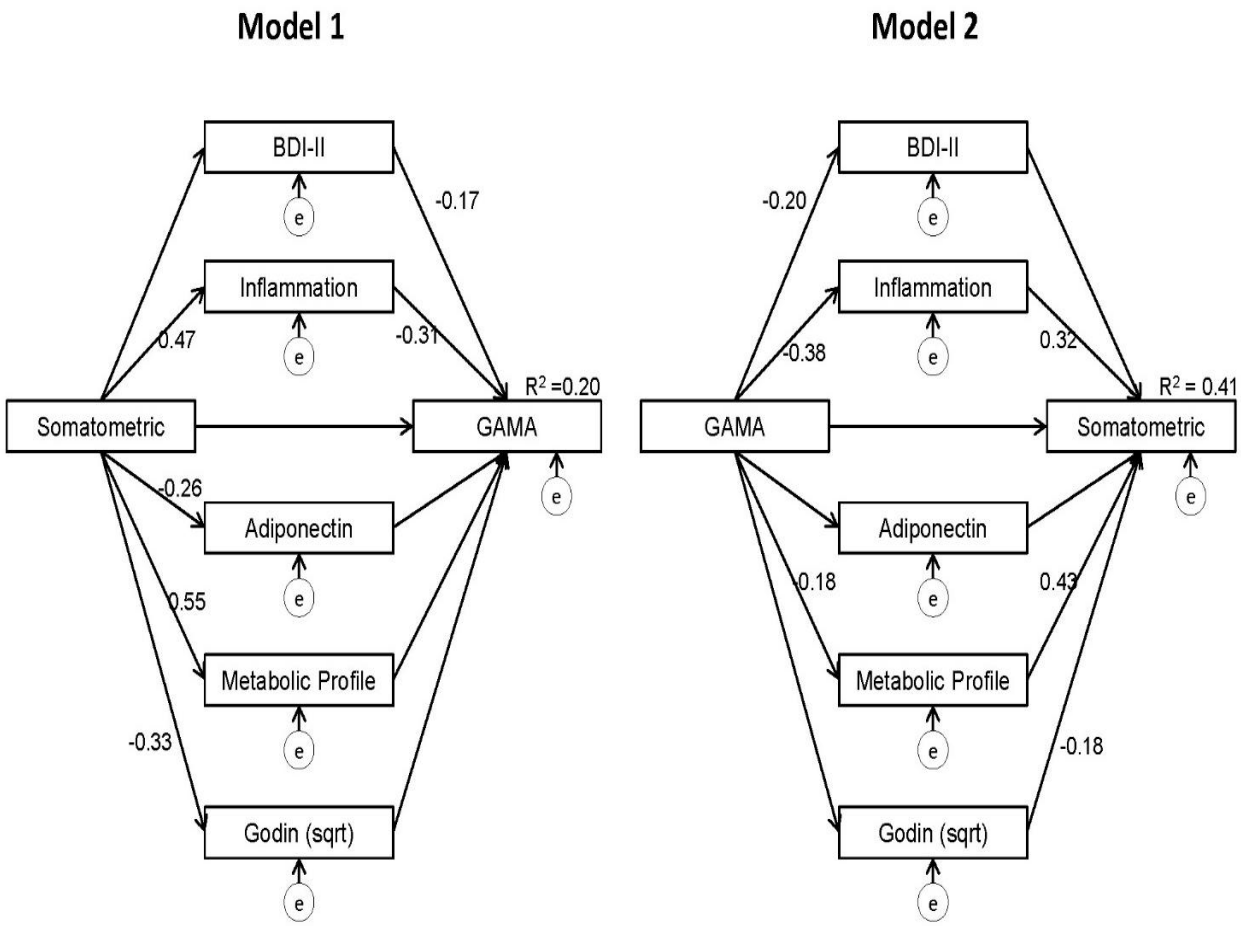

Figure 14. Comparison of the two alternative path models: Model 1 examines the impact of obesity (somatometric) on general cognitive ability (GAMA) while Model 2 tests the reverse path with general cognitive ability resulting in obesity through psychological, inflammation, and physiological parameters. Significant standartized coefficients ($p < 0.01$) and R-squared values are shown. Somatometric = composite index BMI, WHR, BF%; Inflammation = composite index hs-CRP, ESR, fibrinogen; GAMA = General Ability Measure for Adults (raw score); Metabolic Profile = HOMA-IR; Godin (sqrt) = Square root transformed Godin raw scores; BDI-II = Beck Depression Inventory II total score.

to the presence of minimal bias. Specifically, the bias of the chi-square statistic was equal to zero in terms of probabilities of rejected chi square values and the actual estimates on the chi-square values between the expected mode (with 10df) and the observed bootstrapped model was equal to 0.140. With an expected RMSEA of .059 estimates were equal to .067 suggesting a bias of .008, which was negligible. Last, with regard to the mean square error of the path estimates, it ranged between .0044 and .0079. Thus, all power analysis results corroborated with the premise that 180 participants were sufficient to obtain solutions with valid path estimates, and proper rejection rates of the chi-square statistic.

5.3 Does the effect of inflammation depend on other factors?

In these analyses we assessed interactions between psychological, life style, and metabolic parameters as modifiers of the direct and/or indirect (via inflammation) effects of obesity on cognitive function. Moderating effects (α_1X*W and b_1X*W terms in Equations 1 and 2) failed to reach significance for all variables (BDI-II, STAI-T, Godin, adiponectin, HOMA-IR) with the exception of obesity group. This was largely expected given the scarcity of zero-order correlations (see table 4) of the proposed moderators with GAMA (with the exception of a small correlation with BDI score, r=-0.21), somatometric index (with the exception of HOMA-IR with somatometric: r=0.38 and adiponectin with somatometric: r=-0.24), and inflammation (with the exception of HOMA-IR with inflammation: r=0.26).

The model including obesity group as a moderator was significant, R^2=0.19, F(5, 174)=9.80, p=0.0001, revealing a significant moderating effect of obesity group on the association between body weight/fat content and inflammation, α_1=0.39, SE=0.10, p = 0.0002. In separate mediated regression analyses performed for each obesity subgroup the presence of significant mediated effects of inflammation were established only for obese

participants as shown in Table 5. These effects persisted after controlling for demographic variables.

Table 5.

Direct and indirect effects of body weight and fat content on problem solving ability (GAMA total score) through systemic low-grade inflammation for each obesity subgroup

Covariates	R^2	Direct effect (c1')	α	b	Indirect effect[1] CI and normal theory test
Normal-Weight	0.07	-4.72	0.04	-1.61	-0.64 (0.43)
		(2.91)	(0.13)	(2.46)	CI: -1.51 to 0.39 z = -0.16
Overweight	0.01	-0.96	0.20	-1.26	-0.26 (0.58)
		(2.81)	(0.24)	(1.90)	CI: -2.84 to 0.38 z = -0.38
Obese	0.27	1.40	0.9	-4.40	-4.02 (1.18)
		(2.16)	(0.24)**	(.96)***	CI: -7.33 to -2.11 z = -2.88**
Obese (with age, education, & gender as covariates)	0.27	0.41	1.01	-3.69	-3.74 (1.39)
		(1.91)	(0.25)***	(1.0)**	CI: -6.80 to -1.48 z = -2.66*

*p < 0.01, **p <0.001, ***p <0.0001. Unstandardized regression coefficients are shown (SE in parentheses). CI: 95% confidence interval for the indirect effect. [1]bM in Equation 2.

Complementary ANOVAs with obesity group (with 3 levels) and degree-of-inflammation group (with two levels through a median split on the inflammation composite variable) as the between subjects variable, revealed a significant main effect of obesity, $F(2,167)=4.36$, $p=0.014$, which was superseded by the two-way interaction, $F(2,167)=5.40$, $p=0.005$. Follow up simple main effects tests indicated that the effect of obesity remained significant only among participants showing relatively high systemic inflammation, $F(2,56)=10.24$, $p=0.0001$ ($p>0.85$ among low inflammation participants). Figure 15 shows that this effect was due to significantly lower GAMA scores for obese as compared to either normal weight or overweight individuals. Moreover, the trend for lower GAMA scores in the obese group was significant only among those participants displaying above average inflammatory indices, $F(1,61)=22.66$, $p=0.0001$ ($p >0.83$ among normal weight and overweight individuals). These results persisted after controlling for demographic variables (age and education level), HOMA-IR, anxiety and depression symptoms.

A similar set of analyses examining the effects of obesity (with 3 levels) and metabolic profile groups (with two levels through a median split on HOMA-IR) failed to reveal a main effect of metabolic profile group or a two-way interaction.

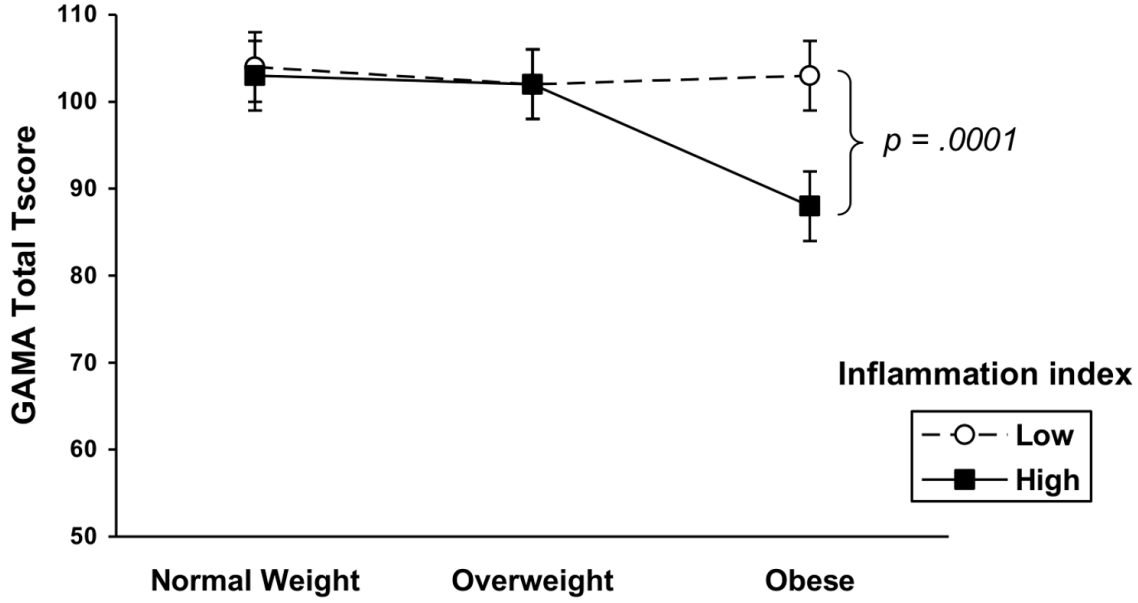

Figure 15. GAMA total standard scores as a function of obesity and inflammation severity group. Bars indicate standard error.

6. Discussion

In this study we assessed the association between obesity, low grade inflammation and cognitive ability in a community sample of young and middle-aged Greek adults free of any obvious medical or psychiatric diseases and grouped as per their BMI. Firstly, our results showed an inverse association between elevated BMI and cognitive performance -using a test of non-verbal logical reasoning ability and fluid intelligence- confirming previously published reports. More specifically, obese participants displayed significantly poorer performance compared to age-matched overweight and normal-weight persons. The novel finding of this work is that obesity-linked chronic low grade inflammation, the principal cause of all metabolic consequences of obesity (insulin resistance, Diabetes Mellitus, atherosclerosis, etc) appears to be directly associated to cognitive defects as demonstrated by both group-level analyses and mediated regression models.

6.1 Integration of the main finding (CLGI mediating role in the obesity-fluid intelligence inverse association) in the current inflammation-obesity literature

It is now increasingly recognized that the deleterious effects of obesity on cognition arise much earlier than previously thought and are not solely mediated by the commonly seen clinical consequences of obesity, such as hypertension, diabetes and atherosclerosis[285]. Instead these effects may result from obesity-related early pathophysiological consequences on innate immunity[286] which, in turn directly harm the central nervous system (CNS).

Cognitive impairments due to inflammation within the CNS have been long recognized in many domains, including learning, memory and attention[287]. For instance, a single LPS intracerebroventricular infusion in mice is visualized in the cortical tissue

microarray analyses not only as an augmentation in the gene expression associated with inflammation but also as a substantial downregulation in genes well recognized as learning and memory mediators[288]. A variety of neuroinflammation-induced mechanisms imposing cognitive and behavioral changes have been identified, such as the above mentioned regulation of gene expression[288,289], as well as alterations in neuronal function, reduced neurogenesis and impaired long-term potentiation[290]. However, in regard to peripheral inflammation, though it has been repeatedly observed that it is also capable to generate cognitive dysfunction as seen in acute infections[291] and recent surgical procedures[292], the brain was thought to be privileged shielded against peripheral immune activation by the blood-brain barrier (BBB). Still just like central administration, systemic LPS has been found to produce deficits in working memory in rodents[293] and the cognitive impact of peripheral inflammation is believed to occur in direct association with proliferation of inflammatory agents within the CNS[294], during situations like sepsis or chronic repeated stress, believed to effectively yield the BBB defense[295].

The obesity related CLGI in peripheral tissues and the circulation was established some time ago[169] yet in support of the results of our study, evidence deriving from animal models showing that obesity can also eventuate in central inflammation is a relatively recent one. High-fat diet-induced obesity was found to result in inflammation-mediated harmfull effects in the hypothalamus[296] and peripheral inflammation due to maternal obesity as a result of high fat diet can be transferred to offspring's brain, resulting in increased microglial activity (the brain’s resident macrophages) in the hippocampus at birth, elevated pro-inflammatory cytokine responses in adulthood, anxiety, and spatial learning difficulties[297]. In another study, mice subjected to a very high fat lard diet (60%) presented with weight gain exhibited areas of brain inflammation associated with poorer performance on a challenging

maze task, compared to mice administered a high fat, Western diet (41% fat) resulting in weight gain but not in brain inflammation[298]. Taken together, these experimental findings support the notion that CLGI constitutes a pathway via which obesity causes impaired cognition much earlier and independently of the other obesity-induced comorbidities.

Molecular pathways linking high fat diet/obesity to feeding-metabolism regulation as well as cognitive dysfunction are currently under thorough investigation. It has been proposed that cafeteria-diet may fracture the BBB in the hippocampus in rats through downregulation of mRNA expression of tight junction proteins, particularly Claudin-5 and -12, in the choroid plexus[299]. Consequently, elevated levels of circulating free fatty acids, pro-inflammatory cytokines, chemokines and immune cells (all elements of the systemic CLGI profile) may infiltrate the brain. Areas such as the arcuate nucleus of the hypothalamus and other circumventricular organs, believed to be less equipped with an effective BBB have also been proposed to easier grant access to such potentially damaging circulating factors[300]. In this way TLR4 receptors, known to recognize both LPS and extracellular lipids as pro-inflammatory factors[301,302], may be exposed to the presence of systemic free fat acids accumulation due to prolonged high fat feeding and their activation might mark the commencement of the inflammatory cascade within microglia and astrocytes[303]. Likewise, proinflammatory cytokines may also set in motion cytokine receptors[304]. As a result, a local hypothalamic inflammatory milieu is thought to be formatted, echoing the perpetuated systemic CLGI. Importantly, this central inflammation can actually contribute to leptin and insulin resistance, making them less able to suppress hunger and feeding, thus favoring weight gain and sustenance of the buildup body weight[296,305]. Moreover, very recent studies add up to the above findings by molecularly depicting in the brain, the long clinically observed associations between different dietary composition, inflammatory and cognitive

outcomes[306]. Maric et al. (2014)[307] showed that after 8 weeks, hypothalamic inflammation was more enhanced in mice fed a diet rich in saturated fats in comparison to mice fed unsaturated fats, while notably a similar pattern was seen for saturated fats from different sources, with those deriving from animal fat (butter) exhibiting a more prominent inflammatory hypothalamic response in comparison to saturated fats from plant fat (coconut oil)[307]. The specific mechanisms behind these differences are currently unknown and most of the work done in this area is naturally based on animal obesity models[308]. Even so, one could theorize that in humans and in regard to the comparison between Westernized diet (one high in saturated fat and refined carbohydrates) and Mediterranean diet (a predominantly plant-based diet, with olive oil being the main type of added fat), the link between the anti-inflammatory[309], satiety promoting[310] and well established in the long run cognitive protective properties[311] of the latter, may well be literally "crossing" through the hypothalamus.

Therefore, there is at present good evidence that high fat feeding induces inflammation within the hypothalamus. Yet, whether inflammation diffuses to –and to which- other extra-hypothalamic brain regions is currently less studied[296,303]. Some recent experimental data point to this direction and also seem to highlight duration of the rich fat diet exposure as a highly important factor in these regard: inflammation occurrence in the hypothalamus of mice has been found to settle as early as three days to three weeks after the initiation of the high fat dietary regime and to spread into extra-hypothalamic regions after continuation of this regimen for more than eight weeks[312]. Inflammatory effects have been recognized in the frontal cortex on high fat diet fed mice after 14 weeks compared to controls[313] in the hippocampus after 20 weeks[314,315] and widespread in the neocortex after 5 months of exposure[316].

It is well known that frontal lobe integrity (at least in humans) is for executive functions and fluid intelligence as largely essential[270] as hippocampus integrity for good learning and memory functions[317]. Neuropsychological research has repeatedly shown that measures of fluid intelligence, purported to be mainly mediated by executive functions in frontal lobe regions of the brain, is less resilient to physiological challenges such as physical damage and ageing than their crystallized equivalents (crystallized intelligence is highly based in explicit memory)[318]. In our study this is also confirmed for another physiological challenge, that of obesity and its innate immunity activated pathophysiological consequences. Though highly premature and based only on animal work, we could not avoid but notice that the above "time-table" of experimental inflammatory diffusion in the brain (after hypothalamus, frontal lobes are the first to appear affected, and then hippocampus) seems to follow an analogous pattern with the one seen in obesity-cognition relationship examination: lower scores in measures of fluid intelligence (as shown in our study) and our free of obesity evident medical conditions sample) and executive function (in other studies[157–160]) seem to be a recurrent finding among ostensibly healthy obese subjects, while memory and learning problems are not as robustly evident in such samples[151].

Keeping in mind the close functional connection of fluid intelligence and frontal lobes, there are further data from the obesity related literature that tie in, both with our main finding of the CLGI mediating role in the obesity-fluid intelligence negative association, as well as the above presented findings of high fat feeding and consequently peripheral inflammation being capable to form a central brain inflammation in the hypothalamus and possibly over time in other brain areas too. Inflammatory markers have been linked with reduced total brain volume[319], a marker of atrophy.

Such kind of brain structural changes have also been detected in obese individuals, providing further evidence that neuronal degradation, possibly due to inflammatory processes, is highly implicated in the obesity-cognition relationship[320]. Lower brain volume has been associated with obesity in many different populations such as in either already cognitively challenged MCI and Alzheimer patients[321], in cognitively intact elders[322] or more significantly in healthy middle-aged obese adults irrespectively of their age and other relevant clinical variables[161,323,324]. The brain areas discovered to be affected are of great interest, especially under the light of our findings for fluid intelligence obesity induced impairment. White matter integrity seems to be ruptured throughout the brain[325,326], but elevated BMI is also reportedly linked to reduction in focal gray matter volume and enlarged orbitofrontal white matter, particularly in the frontal lobes[327]. Functional exploration of the obese brain has provided us with similar results: higher obesity indices associated with decreased regional blood flow[328] as well as reduced brain metabolism[329] in the prefrontal cerebral cortex of otherwise healthy obese adults.

Overall, both in neuropsychological based (like ours) and experimental or imaging studies as those presented above, frontal lobes appear particularly prone to the adverse physiological effects of obesity. If we built on the working hypothesis that obesity related inflammatory processes are in action here, the selective vulnerability of this brain region may be attributable to a variety of underlying mechanisms. A denser expression of inflammatory cytokines in this area may explain the above observations. For instance, IL-6 m-RNA and protein in rat brain were more plentifully discovered in the hippocampus and cortex and with firmer expression in neurons than in astrocytes or microglia[330]. More evidences on differences in the brain allocation of inflammatory cytokine expression may give us more insight in the purported inflammatory effects on certain and not other

cognitive domains (at least at the beginning of the inflammatory process). Of course, other mechanisms must be almost certainly contributing conjointly to this inflammatory effect and research in this field continues.

Hence, as in the general population, measurements of lowered cognitive performance and brain atrophy findings are strong predictors of future cognitive decline and dementia advent[331,332], such early signs of both in obese middle aged adults suggest that this population is already at a greater risk of neurocognitive deterioration.

On the other hand, progressive atrophy and cognitive problems of a relatively subtle nature are characteristics of normal aging too. Namely, normal aging is often accompanied by impairments mostly in the frontal-subcortical brain functioning[333] cognitive declines predominantly in processing speed and executive functioning[334–336]. Episodic memory is also affected but semantic memory and language are rarely influenced[287]. This pattern of cognitive decline seems to closely resemble the one seen developing languidly throughout the lifespan in association to obesity (in younger ages though). For instance, higher adiposity in children and adolescent has been consistently linked to poorer executive function, inhibitory control and attention but not to worse memory and learning performance[337,338]. However, in many of the relative studies in middle aged individuals, indications for memory and learning problems seem to be further added to executive impairments[151]. Apart from those shared cognitive characteristics, aging and obesity both appear to be situations predictive of increased vulnerability to situations closely related to brain health, such as traumatic brain injury[339] and stroke[340–342] (for stroke independently of diabetes, hypertension, or hypercholesterolemia), with slower recovery and more complications at occurrence[343]. Added to innumerous study observations of the obesity's capability to aggravate the severity of other common age-related diseases like hypertension and

myocardial infarction, it has been proposed that obesity is actually an early-onset cognitively aging process[287].

In this direction, we were interested to determine if the magnitude of the purported effect of obesity on cognition varies with BMI. According to this hypothesis, obese individuals would be more likely to have suffered the subtle but adverse effects of low grade inflammation at a greater intensity and for a longer period of time than non-obese participants, sufficient to incur detectable cognitive impairment. Moderation analyses performed in the present sample (using BMI group as a moderator of the obesity-inflammation-cognition association) suggested that these effects may indeed be stronger among obese individuals, but subgroup sizes were relatively small to allow for firm conclusions to be drawn. Notably, the cross-sectional design of this study does not permit quantification of the inflammation "history" of participants, necessary to establish critical features of inflammation potentially leading to cognitive decline.

Even so, in the long run, persistent through lifetime obesity-induced CLGI is destined to coalesce with further inflammatory processes observed in elderly, independently of participants' earlier weight profile. Indeed, in 2000 Franceschi et al[344] were the first to describe an upregulation of the inflammatory response in the elderly, and coined the term 'inflammaging' to refer to this phenomenon. Inflammaging is now generally recognised as another characteristic of old age as part of the general syndrome of immuno-senescence[345]. This upregulation results in the development of low-grade chronic systemic pro-inflammatory state in the elderly, identical to that due to increased adiposity irrespective of age. As expected, it is characterized by elevation of several interleukins as well as that of the acute phase proteins produced by the liver in response to inflammatory cytokines like CRP. Genetic, environmental and age-related factors contribute to the development of

inflammaging and include polymorphisms to the promoter regions of cytokines, cytokine receptors and antagonists, age-related decreases in autophagy and of course increased adiposity[345]. Whereas our study focussed on adults younger than 65 years (mean age = 38.3 years), it is predicted that obesity will contribute to the worsening of inflammaging in the elderly further impacting on "natural" cognitive decline.

6.2 Examination of factors other than CLGI in the obesity-fluid intelligence relationship

The medical literature suggests that, in addition to the degree of systemic inflammation, obese individuals may differ in other pertinent physiological characteristics as well. A considerable percentage of the adult obese population (up to 20%)[346] appear to be less susceptible to the unfavorable metabolic profile that typically accompanies obesity. "Metabolically healthy" (MHO) as opposed to "metabolically unhealthy" obese (MUHO) have been found to display higher levels of insulin sensitivity, no signs of hypertension, normal lipid levels, low triglycerides, high HDL cholesterol and adiponectin concentrations and carry lower risk for developing type 2 diabetes and cardiovascular disease[347]. It should be noted however that the MHO are characterized by much lower levels of inflammation compared to the other obese individuals[348]. Given our results on the mediating role of inflammation in obesity-cognitive performance decline, it appears reasonable to hypothesize that MHO are less prone to cognitive difficulties compared to MUHO persons. To our knowledge the only study addressing this question[349] did not support this hypothesis, failing to find differences between metabolically abnormal and metabolically normal obese participants on a global cognitive score either at baseline or at the 10 year follow up. However, given that Singh-Manoux et al.[349] did not include measures of inflammation, the potential role of low grade

inflammation could not be assessed in this intriguing obesity phenotype. The small size of the present sample notwithstanding, our group level results do not support this claim, by failing to differentiate between obese persons with mild insulin resistance (inappropriately elevated fasting and postprandial insulin levels) from those exhibiting full-blown insulin resistance resulting in hyperglycemia and clinically evident Diabetes Mellitus.

We also explored the potential role of additional physiological factors, namely that of insulin resistance (HOMA-IR) and adiponectin production, in obesity-related inflammation possibly impacting cognition. However, bivariate correlations between these parameters and GAMA, somatometric index, or inflammation were weak and including them as mediators in the obesity-inflammation-cognition association did not support this hypothesis. Notably, neither HOMA-IR nor adiponectin accounted for significant variability in GAMA scores, contrary to the claim that adiponectin may assume a protective role on cognitive ability as an effective insulin sensitizer[205]. Circulating levels of adiponectin are known to be inversely correlated to insulin levels. Given that adiponectin receptors have been identified in the brain[350,351] this protein may exhibit neuroprotective properties[352,353] in addition to its beneficial physiological properties[205,354]. However, epidemiological studies investigating the association of adiponectin with cognition are to date limited, focusing on elderly populations and presenting controversial results. For instance, in a case-control study of elders aged 70–89 years[355] total adiponectin was neither associated to MCI, nor with vascular dementia in another small sample study of similar design (aged 60-95 years)[356]. Other researchers however, did manage to find significant effects with higher adiponectin levels measured in the plasma and cerebrospinal fluid of both MCI (mean age 74.2) and AD patients (mean age 77.4) compared to normal controls (mean age 77.4)[357], thus associating increased adiponectin to cognitively challenged states. Adiponectin was also recognized as an

independent risk factor for the development of dementia (including AD) in a prospect cohort study of elders with mean age of 72 years, although this effect was restricted to women[358]. On the contrary, in a sample of Japanese elders (aged 62-72 years) a 10mg/l increase in plasma adiponectin was found to have a suppressive effect on MCI emergence, thought only in men[359]. In addition, increased adiponectin was associated with higher scores on a composite index of executive function in a large sample of both men and women (aged 18-86 with less than 10% older than 67)[360]. In clinical practice, weight loss in old age is often a sign of advent dementia and since adiponectin is inversely associated to BMI, it has been suggested that higher levels of this adipokine are a mere correlates of higher incidence of dementia and AD[361] in these samples. However, lower adiponectin levels may actually be caused by already progressing pathological processes, with dementia resulting in weight loss and consequent rise of adiponectin and not the opposite. Adiponectin, in general, is evolving into a adipokine of contradictions with even its link to lower risk for cardiovascular disease being challenged[362–364]. In summary, controversial findings in previous and in the current study stress the need for further systematic investigations of the hypothesized inverse association between adiponectin and obesity-related poor cognitive performance. Given that adiponectin exists as multimeric isoforms comprised of High Molecular Weight (HMW), hexamers and trimers indices of HMW adiponectin or HMW adiponectin/total adiponectin have been suggested as better measures of insulin sensitivity than total adiponectin in obesity, diabetes and cardiovascular disease. In this context, use of HMW adiponectin may better serve the adiponectin-cognition investigation[365].

Other factors presently addressed as potential mediators in our proposed obesity-inflammation-cognition model were symptoms of depression and anxiety. Compromised cognitive function, especially in the areas of sustained attention and mental flexibility, has

been identified as a characteristic of clinical and subclinical depression[258,259]. Moreover, elevated levels of stress and anxiety have been linked to impaired performance on cognitive tasks[260] as well as increased body weight[261]. Thus, psychoemotional well-being, as indexed by the absence of symptoms of depression and anxiety has been implicated as a potential mediator of the obesity-cognitive association[262]. However, self-reported levels of such symptoms did not differ among our three BMI groups, suggesting that obesity was associated with reduced cognitive function in a more direct way, at least in the present cohort. This finding is in contrast with at least one previous report linking self-reported levels of negative emotions to cognitive impairments independently from BMI[262]. Nonetheless, participants in that study were heavily obese women (mean BMI = 43.2 ± 3.8) seeking surgical interventions and, unlike our community dwelling obese group (mean BMI = 34.22 ± 3.7), both their inflammatory and psychoemotional profiles may have been overburdened. Consistent with the null findings of the present study, large cross-sectional studies have also failed to find strong associations between obesity and depression, while it was longitudinal studies that established significant bidirectional links between obesity and depression[366].

Examination of the obesity-cognition relationship critically implicates yet another variable: physical activity. Though obesity assessment may subsume lack of activity, independent measurement of this confounder is even more essential in the cognition research context, as activity level has been proven to be an important predictor of cognitive capacity[263,367,368]. The molecular basis of this association has been the subject of extensive study, revealing that apart from increased synaptic plasticity and enhancement of the underlying systems that support it—such as neurogenesis, elevated CNS metabolism and angiogenesis—moderate exercise has also anti-inflammatory properties[369]. The recent conceptualization of CLGI as the common substrate of all obesity medical consequences (i.e.

glucose intolerance, hypertension etc.) provides an explanation of the remediation role of exercise in a wide spectrum of obesity-induced health problems. Thus, given the important role of physical activity on brain function, our finding of the mediating role of CLGI on cognitive functioning is even more important: in our study, assessment of leisure-time physical activity in this community dwelling sample showed a trend of lesser activity as BMI increased, yet group differences did not reach statistical significance. This may have been an artifact of the measurement scale used for physical activity, resulting in a severely positively skewed Godin scores, given that—unfortunately but not surprisingly—most of the participants reported zero leisure time physical activity over a typical week period. This underlines the fact that the vast majority of our sample, independently of their present BMI status, did not benefit from the neuroprotective effects of exercise. This is crucial as it indicates that a highly effective innate neuroprotective mechanism is kept idle, perhaps allowing obesity-induced CLGI to impact brain physiology and, in the long run, cognitive integrity, independently of the presence or not of obesity-induced co-morbidities.

6.3 Strengths and limitations of the study

In a very recent literature review Prickett et al.[370] readdress the relationship between obesity and cognitive function in mid-life (18–65 years of age) and question whether there is indeed evidence that this association is independent of obesity-related comorbidities. The review suggests that there are inconsistencies in this line of research possibly related to neglect of confounds relevant both to obesity and cognitive function (i.e. age, education, depression and CVD risk variables), differences in exclusion criteria (i.e. neurological diagnoses, substance use and head injury), small sample sizes, and occasional use of normative data instead of control groups for cognitive evaluation (a problematic

methodology as different tests use different normative samples, with unknown somatometric characteristics). The present study was designed to address several such confounders, employing a reasonably large final sample (N=180), statistical adjustment for age and education level across weight groups, utilization of the Charlson Index for quantification of comorbidity burden (including CVD factors), and careful screening of neurological, psychiatric or brain injury history of prospective participants. Estimation of socioeconomic status, though relatively crude (due to cultural inconvenience of income inquiry in a more direct way) was also thought to be important in this obesity-cognition relationship as social class is positively associated with cognition[371] and negatively associated with BMI[372]. Additionally, taking into consideration the inherent shortcomings of the BMI index for obesity assessment, two more obesity indices were employed: total body fat percentage and WHR respectively. We further, validated the BIA measure of total body fat against the more robust DEXA assessment. The creation of composite somatometric, as well as inflammation variable, did not only simplify the statistical analysis but also guarded the results against Type I error.

However, the study suffers certain weaknesses. An important limitation was that the sample consisted mainly of women, preventing exploration of potential sex differences on the proposed impact of obesity and associated low grade inflammation on cognitive ability. In the current sample, however, there was no evidence of an effect of gender on the relation between obesity and cognition. Furthermore, cognitive changes during the menstrual cycle were not considered in the analyses[373], although participant recruitment and testing schedules should have ensured random distribution of such effects across BMI groups.

A second limitation of the present study was reliance upon a single measure of cognitive ability, while earlier studies focusing exclusively on the obesity-cognition link

examined this association more thoroughly, utilizing extensive test batteries that address specific cognitive domains. In this context, it was fortuitous that significant effects of obesity and inflammation were found on a measure designed to assess general cognitive ability in the form of fluid intelligence. The sensitivity of GAMA to the effects of obesity and inflammation are not surprising, however, in view of (a) the very high correlations between GAMA scores and, primarily, performance IQ as measured by comprehensive batteries[266,268], (b) that adequate performance on this task requires reasoning ability, as well as cognitive flexibility, given the variety of alternating logical problems featured and, (c) that GAMA is a timed task, rendering performance sensitive to individual differences in processing speed. Notably, both cognitive flexibility and processing speed are particularly susceptible to diffuse brain insults.

It should further be noted that other commonly used measures of GLGI, such as pro-inflammatory cytokines (e.g., IL-6), were not explored in the present study in view of extant evidence that elevated C-reactive Protein (CRP) is the most robust marker of chronic low grade inflammation of obesity an insulin resistance[374–376]. The fact that the vast majority of reports of chronic low grade inflammation of obesity use this marker, makes the current data comparable to the published literature[230,232,377,378].

Perhaps the most critical weakness of the current study is the cross-sectional nature of the data, which rendered them incapable of providing a strong test for the directionality of the obesity-inflammation-cognition relationship. Cognitive flexibility and logical reasoning ability, which are considered among the key components of fluid intelligence, are in principle important determinants of everyday decision making, and are likely involved in the adoption of healthy lifestyle and behaviors (nutritional choices and physical activity)[241,242]. Impairments in such abilities may explain obesity development through poor health choices

while the accumulation of body fat and the ensuing low-grade systemic inflammation may account for further cognitive decline. This hypothetical cycle of events may also explain the long term failure of common obesity prevention and treatment strategies (information on healthy eating choices, encouragement of physical activity and appropriate diet)[379]. While longitudinal evidence is required to clarify this issue, structural modeling of the present cross-sectional data set provides preliminary support to the notion that obesity adversely affects general cognitive ability through a cascade of physiological events rather than the reverse.

Despite these limitations, we were able to identify cognitive decrements in a carefully screened sample of obese individuals, who were free of other serious medical conditions (e.g. chronic autoimmune or inflammatory diseases) or mental disorders (e.g. depression), and establish a mediating role of chronic low grade inflammation. Baring in mind that obesity often coexists with other medical conditions (e.g., diabetes, hypertension, sleep apnea syndrome) known to be independently associated with cognitive deficits, it is expected that in a consecutive, unscreened sample of obese individuals, more severe cognitive deficits would be documented.

6.5 Implications of obesity-induced fluid intelligence impairment at the individual and societal level

It is important to keep in mind that the present study does not suggest that there is an overall intelligence impairment in the obese, but rather a reduction in performance on a widely-used type of assessment of fluid intelligence. Although, this reduction in performance does not reach clinically significant levels for the majority of participants, it is sufficiently severe to be noted on a single test. At an individual level, deficits in specific low-order

cognitive domains may be compensated in everyday life by other cognitive abilities or behavioral strategies, hence individuals may present a better overall cognitive profile in daily interactions. Memory deficits for example could be compensated by use of mnemonic rules or note keeping. However, poorer performance on a general fluid intelligence test as is the case in this study, implies that individuals of elevated body composition indices are affected in a subtle but quite substantive manner. Logical reasoning and problem solving abilities in abstract contexts, such as those assessed by GAMA, are less easy to compensate for and closely linked to the capacity of the person to make successful everyday decisions, adapt to everyday life challenges flexibly, effectively self-monitor their own behavior and refrain from impulsive decisions and choices. As already mentioned above, in the context of a healthy lifestyle and eating choices, this type of cognitive difficulty could be translated in difficulties in initiating beneficial diet regimes, given that logical reasoning entails the capacity to grasp the "bigger picture" and form new concepts, such as what constitutes or not a healthy diet. On the other hand, cognitive inflexibility, poor self-monitoring and impulsivity could be manifested as difficulties in developing and managing individual diet and exercise plans and in sustaining freshly established healthy habits (e.g. specific health constrains).

Research has documented that when cognitive recourses diminish, heuristic based procedures tend to dominate individual choices[380]. This, in synergy with the fact that eating decisions in particular are mostly speedy reactions[381] and largely defined on habitual grounds[382] makes it more likely that food consumption is more of an automatic response than a conscious goal-directed decision[383]. Thus, individuals with obesity-induced, "dampened" cognitive defenses are even more vulnerable to impulsive, nearly unconscious food consumption as well as to alluring external (sight of food, savory aroma) and internal (palatability) cues.

This population might be more susceptible to maladaptive eating patterns in yet another way. Unimpaired cognitive resources have been implicated in effective emotional regulation, a dynamic system that operates both consciously and unconsciously to monitor emotional states and responses in everyday life and engage specific strategies in order to maintain, alleviate or intensify these states[384]. As a self-regulatory process, emotion regulation may control the affective processes that relate to eating and especially "comfort" food consumption. Consequently, findings of fluid intelligence problems in obese may be reflected in an inability to reserve inappropriate but compelling habitual emotional-induced eating responses[383]. Those effects are further amplified by the hedonic characteristics of food rich in fat, sugar and salt (that make them highly palatable), which stimulate the brain reward circuits[385]. Given that westernized environment is a highly obesogenic one (involving ease of access to abundant food of high caloric value, sedentary lifestyle, chronically stressful conditions in a sleep-deprived 24/7 philosophy schedule) obese individuals are trapped in a vicious circle, whose cognitive ramifications are only presently emerging.

The above remarks may raise concerns at an individual level, but from a macroscopic point of view an even more worrisome perspective is revealed. As average lifespan continues to climb, it is becoming increasingly obvious that age-related diseases constitute a growing proportion of social and healthcare burden. It follows that along with longevity, high quality of life is pivotal and this is largely defined by the ability of independent living, a principally cognitively dependant possibility. However, as obesity rates continue to proliferate and increasingly infiltrate ever younger ages, accumulating effects of obesity-related CLGI may significantly contribute to the dementia epidemic.

Middle-aged adults, the population targeted in this study, are not only those to grow into future elders but also those to nurture the next obese generations as parents. This is

particularly important in view of: a) evidence showing that weight loss reverses the deleterious inflammatory profile of obesity and potentially prevents acceleration of future age-related cognitive decline and b) research in childhood obesity has shown that effectively treating parents for obesity may be sufficient to impact offspring obesity issues[386].

6.6 Future directions

CLGI, as the principal component in the development of medical pathologies accompanying obesity, is now also implicated in early-onset neurocognitive decline, and emerges as a promising therapeutic target. Though it may be argued that research has not yet firmly established the magnitude of its independent impact on cognitive outcomes, given the obesity proliferation, CLGI may be highly prevalent in the population posing significant public health risks. Future studies with larger samples of both sexes as well as use of a more thorough neurocognitive evaluation are needed to replicate our findings and determine if the results concerning CLGI are different for specific cognitive domains or sexes. Of great interest is also the degree and exposure duration required for the obesity-related inflammation burden to impact cognition. Longitudinal studies are essential in this direction, taking into account fluctuations in inflammatory processes associated with fluctuations in body weight, often seen in persons repetitively struggling with various diet schemes. This could prove especially challenging as losing weight may suppress CLGI but it may also promote other inflammatory reactions, especially if extreme weight reduction regimes are enacted.

There is some evidence that the neuropsychological sequelae of obesity may be partly reversible. Thus, long term monitoring of an obese population with well-established baseline cognitive capabilities, is necessary in order to evaluate patterns of intra-individual

variations in cognitive performance associated with somatometric and physiological indices and determine the optimal degree of weight reduction needed for any beneficial effects on cognition to take place. Long-term longitudinal data would make it possible to estimate the effect of aging per se as well as the indirect effects of aging on the levels and impact of potential neuroprotective agents. In this regard childhood obesity is particularly important. Maturation of executive function, which is known to evolve well into adolescence[338], may be especially hampered by obesity-related CLGI. Furthermore, loss of weight in elders that often signify the clinical onset of dementia, also point to the direction of critical developmental points in relation to inflammatory processes and obesity interactions.

Of course, reduction of inflammatory signaling through lifestyle modifications known to reduce weight and cardiovascular disease (caloric restriction and/or healthier diet regimen, physical activity), faces the same old challenge: inability of the targeted population to maintain such changes over time. Identification of obesity related cognitive impairment opens a novel and exciting research prospective in this respect. Along with classic interventions, addressing cognitive deficits through cognitive remediation therapy as proposed by Smith et al.[151] may improve one's ability to attend, remember and think clearly in relation to eating behavior. Cognitive remediation or cognitive enhancement is an empirically validated intervention, designed to enhance adaptive cognitive skills and improve functioning[387]. These efforts involve complementary strategies: cognitive remediation techniques—through drills and exercises, in paper and pencil or computerized form, individualized or group-based, and support in developing compensatory, adaptive strategies. Such approaches are currently used widely in the management of conditions involving cognitive deficits such as attention deficit disorder, brain injury, and schizophrenia spectrum disorders[387]. More recently, cognitive remediation programs have been applied to mood

disorders[388] and anorexia nervosa[389]. As both conditions adjoin obesity, encouraging outcomes in these areas, render cognitive remediation a promising tool for excess adiposity treatment.

In conclusion

In a country such as Greece that until recently followed a beneficial Mediterranean diet for weight control, incidence of obesity rises at an alarming rate both in adults[390] and in children[391], further adding to concerns regarding obesity-related cognitive dysfunction. Enhancing our understanding of the underlying neuronal, endocrinological, neuropsychological mechanisms and their complex interactions, could directly improve strategies for obesity treatment or prevention. Studies such as this, revealing putative pathways between obesity-related early pathophysiological consequences on innate immunity and cognitive impairments may help in this direction.

7. Highlights

- *Obesity is sometimes associated with impaired cognitive performance*
- *Obesity-induced medical pathologies (i.e. insulin resistance, diabetes mellitus, dyslipidemia, arteriosclerosis, hypertension, obstructive sleep apnea syndrome) were early recognized as major causative pathways leading to cognitive degradation*
- *Growing evidence supports the notion that independently of those physiological consequences, obesity is associated to impaired cognition*
- *Development of chronic low grade inflammation (CLGI) represents the earliest consequence of obesity thus emerging as a serious candidate directly linking obesity and its neuropsychological sequelae*
- *Results of this study confirmed an inverse association between elevated BMI and cognitive performance, using a test of non-verbal logical reasoning ability and fluid intelligence*
- *Obese participants displayed significantly poorer performance compared to age-matched overweight and normal-weight persons*
- *The association between obesity and fluid intelligence impairment was mediated by CLGI, independently of physiological (metabolic dysfunction indices and adiponectin), psychological (anxiety and depression symptoms) and life style (exercise) factors.*
- *Comparison of two alternative pathways regarding the direction of the obesity-cognition association revealed that a direct effect of obesity on cognition through inflammation fitted the current data significantly better*

than the reverse model which suggested that poor cognition might lead to fat accumulation (through adoption of poor health choices)

- *Results support the hypothesis that reduced general cognitive ability is linked to obesity, an adverse effect mainly mediated by obesity associated activation of innate immunity*
- *Contrary to earlier belief, the obesity associated neurocognitive impairments might be established earlier than the onset of overt medical obesity comorbidities*
- *Implication of obesity-induced inflammatory processes in cognitive impairment supports the notion that obesity is actually an early-onset cognitively aging process*
- *Adult and childhood obesity proliferation in Greece is rising, further adding to concerns regarding obesity-related cognitive dysfunction and its potential role in the rising incidence of dementia in the elderly*

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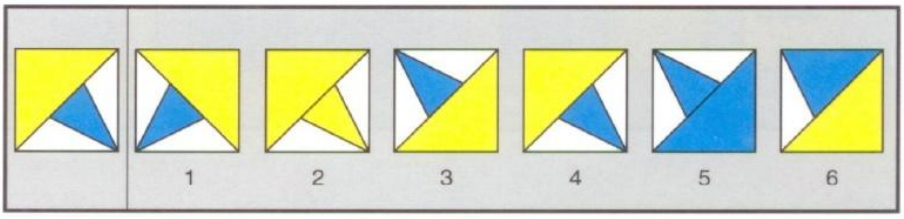
9. Appendix

Part 1. General Ability Measure for Adults: problem paradigms

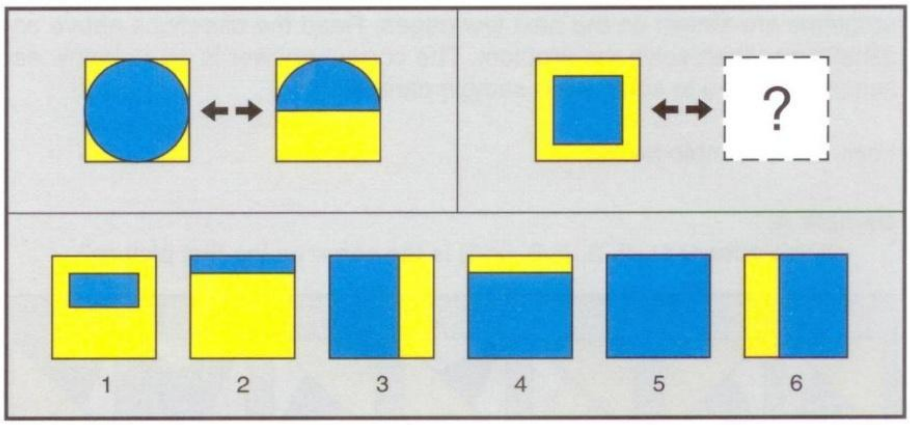
Matching Subscale

Look at the sample below. Which answer (1,2,3,4,5 or 6) is the same as the first picture?



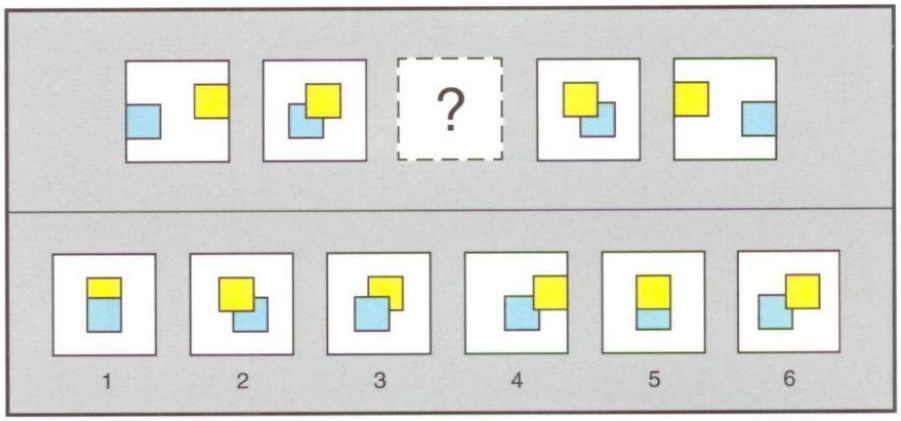
Analogies Subscale

Which answer (1,2,3,4,5 or 6) goes on the question mark?



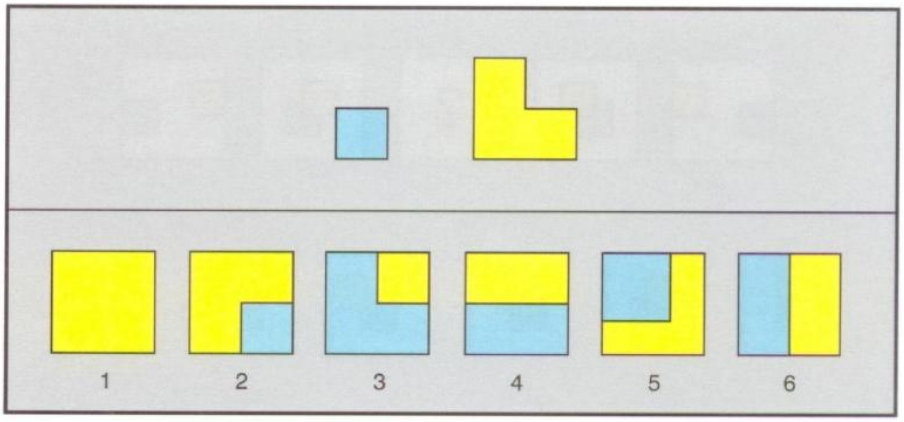
Sequence subscale

Which answer (1,2,3,4,5 or 6) goes on the question mark to complete the pattern?



Construct Subscale

Which answer (1,2,3,4,5 or 6) can be made with the shapes in the top box?



Part 2. Published article (British Journal of Nutrition)

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doi:10.1017/S0007114514002207

The association between obesity and fluid intelligence impairment is mediated by chronic low-grade inflammation

Eirini C. Spyridaki[1], Panagiotis Simos[2], Pavlina D. Avgoustinaki[1], Eirini Dermitzaki[1], Maria Venihaki[1], Achilles N. Bardos[3] and Andrew N. Margioris[1]*

[1]*Laboratory of Clinical Chemistry – Biochemistry, Department of Laboratory Medicine, School of Medicine, University of Crete, Heraklion GR-71003, Crete, Greece*
[2]*Department of Psychiatry, School of Medicine, University of Crete, Heraklion, Crete, Greece*
[3]*School of Applied Psychology and Counselor Education, University of Northern Colorado, Greeley, CO, USA*

(Submitted 30 November 2013 – Final revision received 1 July 2014 – Accepted 7 July 2014)

Abstract

Published evidence suggests that obesity impairs cognition. Development of chronic low-grade inflammation (CLGI) represents the earliest consequence of obesity. The present study investigated the association between obesity and fluid intelligence impairment and assessed the potential mediating role of CLGI and psychological (depression/anxiety symptoms), lifestyle (exercise) and physiological (metabolic dysfunction indices) factors in this association. Clinically healthy participants (*n* 188), grouped as per BMI, underwent cognitive (General Ability Measure for Adults), psychological (Beck Depression Inventory-II and State-Trait Anxiety Inventory) and activity (Godin leisure-time physical activity) measurements. Biochemical parameters included the following: (a) indices of CLGI (high-sensitivity C-reactive protein, erythrocyte sedimentation rate and fibrinogen); (b) insulin resistance (Homeostasis Model Assessment of Insulin Resistance index); (c) adiposity (plasma adiponectin). An inverse association between elevated BMI and fluid intelligence was observed, with obese participants displaying significantly poorer performance compared with age-matched normal-weight peers. Structural equation modelling results were consistent with a negative impact of obesity on cognition that was mediated by CLGI. The results of the present study support the hypothesis that reduced general cognitive ability is associated with obesity, an adverse effect mainly mediated by obesity-associated activation of innate immunity.

Key words: **Obesity: BMI: Fluid intelligence impairment: Chronic low-grade inflammation: Adiponectin**

Obesity causes multiple chronic metabolic disturbances including insulin resistance, diabetes mellitus, dyslipidaemia, hypertension, obstructive sleep apnoea syndrome and arteriosclerosis, which are further associated with impaired cognition[1,2]. However, there is growing evidence that the poor performance of obese individuals on several neuropsychological tests may occur independently of the direct physiological consequences of obesity[3]. Cognitive decrements have been reported for memory[4,5] and executive functions, such as those commonly associated with fluid intelligence[3,6–8]. The risk of poor executive cognitive function has been found in one study[9] to be four times higher in obese individuals than in non-obese individuals, independently of their demographic and medical characteristics. Furthermore, it has been suggested that the performance differences found in overweight and obese adults compared with normal-weight peers may be restricted to executive tasks after controlling for potential confounding factors[10]. Although the physiological consequences of obesity are increasingly better understood, the nature of the association between obesity and cognitive capacity remains unclear. According to one hypothesis, obesity may lead either directly or indirectly to disturbances in brain function manifested by poor cognitive performance. Alternatively, poor executive functions (including planning, cognitive flexibility and logical reasoning ability) may explain obesity development through the adoption of poor health choices given that these abilities are important determinants of everyday decision making (e.g. dietary behaviour, low inhibition of palatable, yet low-nutritional value food consumption, and low physical activity)[11,12].

It is now generally accepted that the development of chronic low-grade inflammation (CLGI) may represent the earliest consequence of obesity significantly contributing to the emergence of

Abbreviations: CLGI, chronic low-grade inflammation; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAMA, General Ability Measure for Adults; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; IQ, intelligence quotient; STAI, State-Trait Anxiety Inventory; WHR, waist:hip ratio.

* **Corresponding author:** A. N. Margioris, fax +30 2810 394571, email andym@med.uoc.gr

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all other obesity-related pathophysiological co-morbidities. CLGI is usually documented by elevation of the levels of acute reactive proteins such as C-reactive protein (CRP; the most conventional and robust marker of CLGI in obesity and insulin resistance[13–15]), serum amyloid A and fibrinogen and those of inflammatory cytokines and chemokines such as IL-6 and TNF-α[16]. Data from several sources implicate CLGI to be involved in cognitive impairments. For instance, high levels of CRP in mid-life may increase the risk for the development of dementia, independently of the development of cardiovascular consequences[17], whereas amelioration of CLGI has been linked to milder patterns of cognitive impairment in dementia-free middle-aged and elderly individuals[18,19]. Raised levels of circulating CRP and fibrinogen and elevated plasma viscosity predict, longitudinally, lower late-life cognitive ability[20]. More importantly, there is increasing evidence linking erythrocyte sedimentation rate (ESR), a non-specific marker of CLGI, to reduced performance in neuropsychological tests, even in healthy young adults[21]. CLGI is the most important cause of obesity-induced insulin resistance, which is, in turn, linked, either concurrently or prospectively, to impaired cognitive performance[22]. Moreover, obesity lowers the levels of circulating adiponectin, which exerts anti-inflammatory as well as insulin-sensitising effects. Recent work[23] on the pathophysiology of obesity has highlighted the potential role of adiponectin as a mediator of obesity-induced CLGI. More specifically, hyperplastic adipocytes in obese individuals undergo a phenotype change favouring the expression of components of the inflammatory machinery, i.e. the toll-like receptor 4, elevation of inflammatory cytokine production and down-regulation of adiponectin production. Lower levels of circulating adiponectin, which is strongly and negatively associated with anthropometric indices of adiposity and fat accumulation, further activate both innate and adaptive inflammatory mechanisms, resulting in insulin resistance and the development of a full-blown metabolic syndrome[24].

The present cross-sectional study examined the association between obesity-linked immune and metabolic effects, including that of adiponectin, and general cognitive capacity. Using data obtained from young and middle-aged Greek volunteers who were largely free of other clinically evident obesity-related medical co-morbidities, the study pursued two specific goals: to examine the possible negative association between body weight/fat content and fluid intelligence, as measured by a non-verbal logical reasoning test, and to compare two alternative path models regarding the direction of the obesity–cognition association, including CLGI as a mediator variable. Importantly, the potential mediating role of CLGI was assessed by controlling for the effects of additional physiological (metabolic dysfunction indices and adiponectin), psychological (anxiety and depression symptoms) and lifestyle (exercise) measures.

Methods

Participants and procedures

In total, 199 participants were recruited through direct contact during regularly scheduled appointments for routine clinical evaluations (e.g. complete blood count or other more specific tests appropriate for their health condition) at primary care facilities (private endocrinology practice and the University Hospital outpatient clinic). The participants were free of major and chronic autoimmune or connective tissue diseases. Other existing medical co-morbidities were quantified using the Charlson Comorbidity Index[25]. Individuals with self-reported history of mental diseases, including depression, and neurological disorders or traumatic brain injury (resulting in >10 min loss of consciousness) were excluded from further analyses (*n* 7). Furthermore, individuals with a recent history of infection (reported or diagnosed during clinical examination) or demonstrating leukocytosis (leucocytes >10·000) were not included in the final sample. Obesity indices, including BMI, waist:hip ratio (WHR) and body fat composition, were measured on site by a trained research assistant in a quiet examination room during a scheduled appointment. The assistant also administered the fluid intelligence test and the self-reported questionnaires and conducted the semi-structured mini-interview on health-related issues (e.g. smoking, alcohol consumption and past medical history).

The participants were assigned to three groups: normal weight (BMI range: 18·5–24·99 kg/m^2); overweight (BMI range: 25–30 kg/m^2); obese (BMI ≥30 kg/m^2). Sample clinical and demographic information is given in Table 1.

The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the University of Crete Hospital Ethics Committee (protocol no. 3842). All participants provided written informed consent following a detailed explanation of the protocol. Participation was voluntary, and the participants were not given financial compensation for their time and effort.

Measures

Cognitive, psychological and activity measurements. The General Ability Measure for Adults (GAMA)[26], developed by one of the co-authors (A. N. B.), is a non-verbal measure of general (primarily fluid) intelligence, independent of verbal factors both in content and in administration, making the test useful for diverse populations (e.g. ethnicity, language and literacy). It consists of sixty-six problems utilising coloured, abstract designs that require the examinee to match a sample design (Matching scale), complete a pair of stimuli through analogy to a model pair (Analogies scale), identify logical sequences (Sequences scale) or combine pieces mentally to form a complete geometric pattern (Construction scale). The correct answer is selected from a set of six choices. Comparison data were available for 453 Greek adults (257 women and 196 men), aged 17– 82 (mean 39·96 (SD 14·47)) years with 2–24 years of formal education (mean 13·09 (SD 3·68) years), recruited from six broad geographical regions in the Greek mainland and islands (296 from urban areas and 157 individuals from rural areas or small towns (defined as population under 10 000)). The sample was divided into nine subgroups representing full cross-over of age and education with a minimum of thirty individuals per group. Education was converted into

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Table 1. Clinical and demographic information for each group of participants
(Mean values, standard deviations and ranges)

	Normal weight			Overweight			Obese		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
n		55			54			71	
Men		7			20			11	
Women		48			34			60	
Marital status									
Single		36			27			26	
Married		16			25			41	
Divorced/widowed		3			2			4	
Type of occupation									
Sedentary		30			24			33	
Manual		4			8			8	
Mixed		21			22			30	
Reported financial status									
Poor		1			3			3	
Average		30			26			42	
Above average		24			25			26	
Age (years)	39·91	9·92	19–54	36·71	10·90	18–64	39·51††	11·38	17–62
Education (years)	16·40	2·79	12–22	15·29	2·60	6–22	13·72**††	2·91	6–22
BMI (kg/m^2)	22·33**	1·76	18·65–24·98	27·37	1·42	25·04–29·86	34·22**††	3·79	30·12–45·88
WHR (cm/cm)	0·79**	0·07	0·65–1·02	0·88	0·06	0·73–0·97	0·89††	0·09	0·69–1·14
Total fat (%)	27·73**	5·80	16·50–40·70	33·47	6·00	21·20–42·30	41·53**††	4·35	28·50–51·52
STAI-T	42·93	7·65	31–61	42·39	8·02	30–63	44·01	8·91	31–69
BDI-II	10·35	7·31	0·00–27	10·81	8·22	0·00–35	12·85	8·40	0·00–48
Godin	27·04	17·99	0·00–65·00	21·81	19·74	0·00–79·00	14·49	13·95	0·00–52·00
CCI									
0		54			51			63	
1		0			3			2	
2		1			0			5	
3		0			0			1	

WHR, waist:hip ratio; STAI-T, State-Trait Anxiety Inventory; BDI-II, Beck Depression Inventory II; Godin, leisure-time physical activity (total raw scores); CCI, Charlson Comorbidity Index.
** Mean value was significantly different from that of the overweight group ($P<0·01$).
†† Mean value was significantly different from that of the normal-weight group ($P<0·01$).

a discrete variable with three levels: 0–9 years of formal education; 10–12 years; 13+ years. Age was also grouped into three levels (17–37, 38–50 and 51–65 years). Raw total GAMA scores were converted into intelligence quotient (IQ)-equivalent scores (mean 100 (SD 15)) adjusting for age and education level. Raw scores on each of the four GAMA subscales (Matching, Analogies, Sequences and Construction scales) were converted into appropriate standard scores (mean 10 (SD 3)). Performance in this test is strongly correlated with scores on more comprehensive IQ measures, such as the Wechsler Adult Intelligence Scale-Revised (WAIS-R)[26]. GAMA correlated 0·74 with WAIS-R performance IQ, 0·65 with WAIS-R verbal IQ, and 0·75 with WAIS-R full-scale IQ. The magnitude of these associations was similar in the presence of acute brain damage (*r* 0·74, 0·71 and 0·81, respectively)[27] and among young adults experiencing academic difficulties (*r* 0 .69, 0·36 and 0·60, respectively[28]). Given that GAMA was originally designed as a measure of fluid intelligence, achieving high scores in the test requires adequate engagement of functions generally considered to be 'executive'[29]. Such presumed, higher-order, yet diverse, cognitive functions serve the ability to coordinate goal-directed thought and action and include complex attention, mental flexibility, inhibition, problem solving and decision making. These functions are believed to be primarily carried out by prefrontal areas[30]. Solving the logical problems in GAMA requires successful, continuous management of working memory resources[31,32] and the ability to switch cognitive strategies while dealing with different types of alternating problems[33,34]. In fact, in the present Greek adult community cohort, performance in GAMA was found to correlate strongly ($r > 0·60$) with such measures. Internal consistency (Cronbach's $\alpha = 0·93$) and test–retest reliability (*r* 0·84; *n* 48) in the same cohort were adequate.

The revised edition of the Beck Depression Inventory-II[35] is a twenty-one-item self-report questionnaire, designed to assess the intensity of Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) depressive symptomatology in clinical and community adult samples. Each item consists of four statements arranged in order of increasing severity on a 0–3 scale (e.g. 0 = 'I do not feel sad' to 3 = 'I am so sad and unhappy that I can't stand it'). The respondents are asked to rate each set of the statements according to how they have been feeling in the past 2 weeks, including the date of questionnaire completion. A total score of less than 14 points indicates minimal depression symptoms, that of 14–19 points indicates mild depression symptoms, and that of 20–28 points indicates moderate depression symptoms, whereas a score between 29 and 63 points indicates severe depression symptoms. The Greek version of Beck Depression

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Inventory-II[36] used in the present study has Cronbach's $\alpha = 0{\cdot}87$.

The State-Trait Anxiety Inventory (STAI, Y form)[37] is a self-report measure of the severity of anxiety feelings in adults. The Greek version of the Trait Anxiety subscale (STAI-T)[38] was used in the present study, assessing more general and long-standing anxiety. Sample items include 'I feel nervous and restless', 'I lack self-confidence' and reverse-scored items such as 'I am content'. Questions are rated on a four-point Likert scale resulting in a score range between 20 and 80 points, with higher scores indicating greater anxiety. Cronbach's α was 0·90.

Leisure-time physical activity was assessed using Godin's self-administered questionnaire[39]. The participants reported the number of times spent in physical activity lasting for at least 15 min in an average week and classified them as strenuous, moderate or light (corresponding to 9, 5 or 3 metabolic equivalents). The total score was derived by multiplying the reported frequency by its corresponding metabolic equivalent value and summing the three products. Test–retest reliability of the total score ranged between 0·62 and 0·81[40]. As with the majority of available self-administered physical activity questionnaires, Godin scores derived from broad community samples demonstrate a somewhat inconsistent validity profile. Correlations between Godin scores and measures of energy expenditure are generally low (r 0·10–0·32), although stronger associations with body fat have been reported[40,41]. In all analyses involving Godin's data, square root-transformed scores were used to correct for significant positive skewness in the data.

Somatometrics. Total height and weight were measured to calculate BMI (kg/m^2). WHR (waist circumference:hip circumference) is commonly used as a convenient index of body fat centralisation (visceral obesity). Waist and hip circumferences were measured at the level of umbilicus and gluteus, respectively. Total body fat percentage (Fat%) was estimated using bioelectrical impedance analysis employing Akern BIA 101 (Akern, S.r.l.). To validate this technique, body fat composition was determined using dual-energy X-ray absorptiometry using Lunar DPX (GE Healthcare) in a random subgroup of the participants (n 23), which along with computed tomography is known to be the most accurate assessment method of body fat[42]. The correlation between bioelectrical impedance analysis and dual-energy X-ray absorptiometry in this subgroup was linear and high (r 0·91).

Biochemical indices. Morning fasting blood samples were collected in a serum-separating tube from all participants, allowed to clot at room temperature for 30 min, centrifuged, aliquoted and stored at −80°C in plastic vials for subsequent measurements. Biochemical analyses were performed at the University of Crete, Laboratory of Clinical Chemistry. Among the volunteers recruited, twelve demonstrated leukocytosis and were excluded from further analyses. The following indices were available for the remaining 180 participants: (a) high-sensitivity C-reactive protein (hs-CRP) measured by immuno-nephelometry assay on a Cobas 6000 analyser with a detection limit of 0·18 mg/l (Roche Diagnostics International, Ltd); (b) fibrinogen; (c) ESR. Insulin resistance was assessed using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index computed by multiplying serum levels of glucose (mg/dl) by those of insulin (μU/ml) and dividing by 405[43]. Finally, total plasma adiponectin was quantified using the Human Adiponectin ELISA Kit (catalogue no.: KHP0041; Life Technologies Corporation).

To simplify the set of regression and path analyses described below, composite indices for somatometric (BMI, WHR and Fat%), and inflammation (hs-CRP, ESR and fibrinogen) markers were assessed, expressed as the mean of the respective Z-scores in the present study sample. An exploratory factor analysis with Varimax rotation on the six measures revealed two factors with eigenvalues >1. Factor 1 was mainly accounted for by variance of fibrinogen, ESR and hs-CRP (factor loadings ranged between 0·68 and 0·83), whereas factor 2 mainly reflected variance of the three somatometric measures (factor loadings ranged between 0·69 and 0·86). Cross loadings did not exceed 0·39. Correlations among somatometric indices ranged from r 0·23 (Fat%–WHR) to r 0·81 (BMI–Fat%). Correlations among inflammation indices ranged from r 0·48 (fibrinogen–hs-CRP) to r 0·56 (ESR–hs-CRP).

Statistical analysis

The first aim of the study was explored through ANOVA on GAMA standard scores with BMI group as the between-subjects variable with three levels (normal weight, overweight and obese). Physiological and clinical variables, for which the three groups should be found to vary significantly, were also entered in a separate one-way ANOVA as covariates in SPSS (version 20; SPSS, Inc.).

The second aim of the study was explored through structural equation modelling analyses comparing the two alternative, non-nested models shown in Fig. 1. Model 1 postulates a direct effect of obesity (somatometric index) on cognition (GAMA total score), whereas model 2 represents the reverse relationship. Each model included a number of parallel mediators representing psychological (Beck Depression Inventory-II and STAI-T scores), lifestyle (Godin's scores) and physiological (HOMA-IR and adiponectin) factors and estimated both direct and indirect associations (i.e. through each of the mediating variables) between obesity and cognition. The two models were directly compared on fit indices calculated in AMOS version 20 (SPSS, Inc.). This statistical technique allows testing of theoretical pathways involving causal relationships and is thus suitable for inferential analysis of cross-sectional data[44].

Results

BMI group comparisons

The series of one-way between-subjects ANOVA confirmed the expected group differences in WHR (F(2,177) = 30·65, P=0·0005, η^2 = 0·261) and Fat% (F(2,177) = 81·03, P=0·0005, η^2 = 0·568). As shown in Table 1, all pairwise group differences

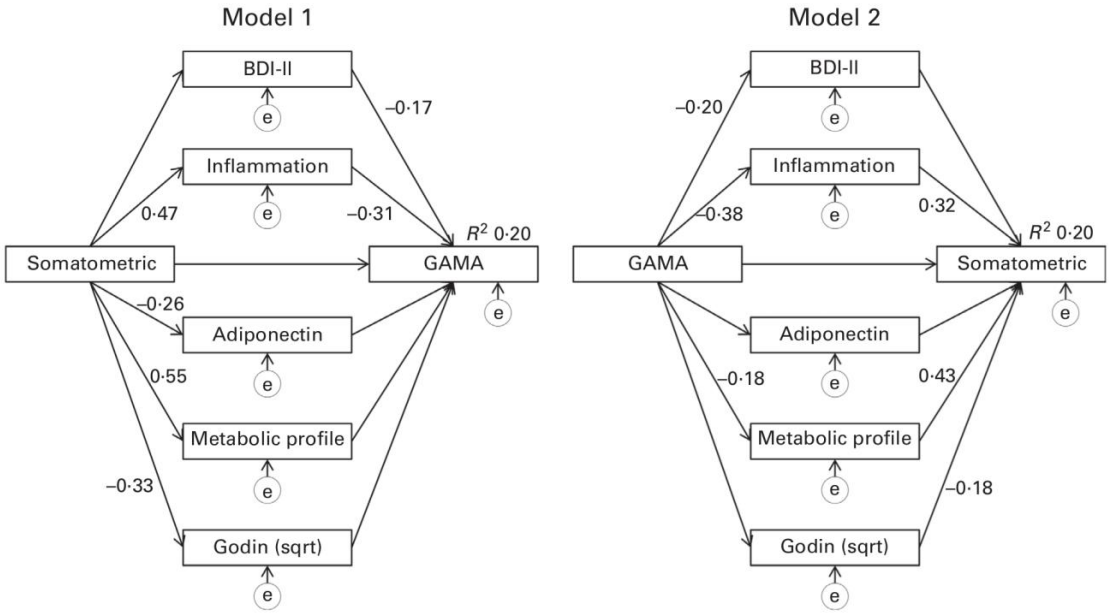

Fig. 1. Comparison of the two alternative path models: model 1 examines the impact of obesity (somatometric) on general cognitive ability (General Ability Measure for Adults (GAMA, raw score)), while model 2 tests the reverse path with general cognitive ability impairment resulting in obesity through psychological, inflammation and physiological parameters. Significant standardised coefficients ($P<0·01$) and R^2 values are shown. Somatometric: composite indices BMI, waist: hip ratio, and Fat%; Inflammation: composite indices high-sensitivity C-reactive protein, erythrocyte sedimentation rate, and fibrinogen; Metabolic profile: Homeostasis Model Assessment of Insulin Resistance; Godin (sqrt): square root-transformed Godin's raw scores; BDI-II: Beck Depression Inventory-II total score.

were significant. Further tests showed that BMI groups did not differ in Beck Depression Inventory-II, STAI-T or Godin's scores ($P>0·5$). The χ^2 tests did not reveal group differences in the distribution of Charlson Comorbidity Index scores, marital or financial status, or type of job. Data on all metabolic and inflammation indices for each BMI group are given in Table 2. In addition to somatometric indices, the three groups also differed in inflammation indices (ESR: $F(2,177) = 14·53$, $P=0·0005$, $\eta^2 = 0·115$; hs-CRP: $F(2,177) = 26·65$, $P=0·0005$, $\eta^2 = 0·218$; fibrinogen: $F(2,177) = 6841$, $P=0·001$, $\eta^2 = 0·07$) and metabolic indices (insulin: $F(2,177) = 13·13$, $P=0·0005$, $\eta^2 = 0·135$; glucose: $F(2,177) = 10\,268$, $P=0·0001$, $\eta^2 = 0·096$; HOMA-IR: $F(2,177) = 12·05$, $P=0·0005$, $\eta^2 = 0·137$; adiponectin: $F(2,177) = 7·74$, $P=0·001$, $\eta^2 = 0·080$). With the exception of adiponectin, the obese group had higher indices than both normal-weight and overweight groups. As expected, the opposite pattern was observed for adiponectin. Given that the proportion of men was higher in the overweight group (37%) than in the normal-weight group (12%) and obese group (15%; $\varphi = 0·213$, $P=0·013$), the analyses were repeated with sex as an additional factor, which failed to reveal any significant main effects or interactions ($P>0·1$).

As the three groups differed in age ($F(2,177) = 5·94$, $P=0·003$), years of formal education ($F(2,177) = 15·21$, $P=0·0005$) and sex distribution, group-level analyses of cognitive ability were conducted on age- and education-adjusted GAMA IQ scores and subscale standard scores. At the group level, the key finding was a main effect of BMI group ($F(2,177) = 7·09$, $P=0·001$, $\eta^2 = 0·083$). Planned pairwise comparisons revealed that the obese group scored

Table 2. Metabolic and inflammation indices for each group of participants
(Mean values, standard deviations and ranges)

	Normal weight			Overweight			Obese		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
ESR (mm/h)	9·24	6·71	1–30	11·88	8·68	3–30	20·01**††	14·99	3–91
hs-CRP (mg/l)	0·85	0·95	0–4	1·53	1·76	0–9	4·66**††	4·39	0–17
Fibrinogen (mg%)	262·38	54·73	151–448	269·34	58·04	145–449	304·64**††	74·30	142–626
Insulin (μU/ml)‡	5·96	3·56	2–18	8·37	3·91	3–23	14·22**††	13·69	1–79
Glucose (mg/dl)‡	88·79	5·53	78–102	91·67	11·59	60–150	97·66**††	12·90	76–152
HOMA-IR	1·27	0·77	0·38–4·24	1·97	1·25	0·65–8·67	3·58**††	3·85	0·27–18·83
Adiponectin (mg/ml)	16·69	6·25	6·23–30·36	15·62	6·36	4·41–30·27	12·53**††	5·40	4·86–30·41

ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance.
** Mean value was significantly different from that of the overweight group ($P<0·01$).
†† Mean value was significantly different from that of the normal-weight group ($P<0·01$).
‡ To convert insulin in μU/ml to pmol/l, multiply by 6·945. To convert glucose in mg/dl to mmol/l, multiply by 0·0555.

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Table 3. Average General Ability Measure for Adults (GAMA) total intelligence quotient-equivalent scores and subscale standard scores for each BMI group
(Mean values and standard deviations)

	Normal weight		Overweight		Obese	
	Mean	SD	Mean	SD	Mean	SD
GAMA	104·38	15·11	101·85	13·77	94·91*†††	15·15
Matching	11·19	2·74	10·70	2·58	8·56**†††	2·89
Analogies	11·19	2·67	10·88	2·71	8·46**†††	2·78
Sequences	10·97	2·67	10·82	2·54	8·67**†††	3·07
Construction	11·06	3·11	10·24	2·77	8·91†††	2·75

Mean value was significantly different from that of the overweight group: * $P<0·03$, ** $P<0·01$ (Bonferroni-corrected).
††† Mean value was significantly different from that of the normal-weight group ($P<0·001$; Bonferroni-corrected).

significantly lower than both the normal-weight ($P=0·001$; Bonferroni-corrected) and overweight ($P=0·029$) groups, which did not differ from each other ($P>0·7$). Main group effects were also significant for each of the four GAMA subscales ($P<0·001$), and pairwise tests revealed a similar pattern of group differences (Table 3). Importantly, group differences in GAMA IQ scores remained significant after controlling for STAI-T, BDI, Godin's and Charlson Comorbidity Index scores, as they did after controlling for metabolic function (insulin, HOMA-IR and adiponectin). However, on controlling for individual variability in the systemic inflammation composite, group differences in GAMA IQ scores were all but eliminated ($P>0·24$). Results were essentially identical when ANCOVA were performed on GAMA total raw scores controlling for participant age and education. Neither the main effect of sex nor the group × sex interaction approached significance ($P>0·8$). Power analyses indicated that for the effect size of group differences observed in the study, the estimated power for detecting significant group main effects ranged between 0·96 and 0·99 at $\alpha = 0·05$ and between 0·84 and 0·99 at $\alpha = 0·001$.

The percentages of individuals with 'normal-range' IQ were 90, 88 and 78 % for the normal-weight, overweight and obese groups, respectively. The remaining participants had estimated IQ scores in the 70–85-point 'borderline' range.

The role of low-grade systemic inflammation

Table 4 reveals a largely expected pattern of intercorrelations between the somatometric, inflammation and cognitive indices (GAMA raw scores). Correlation coefficients were in the moderate range meeting the essential requirement to further assess direct and indirect effects of obesity on GAMA (and the reverse) through inflammation. As shown in Fig. 1, results suggested that model 1, which tested the hypothesis that obesity (somatometric index) affects cognitive ability (GAMA) through inflammation, controlling for psychological, lifestyle and physiological factors, fitted the present data significantly better ($\chi^2 = 9·6$, df = 10, $P=0·48$, normed fit index (NFI) = 0·953, comparative fit index (CFI) = 1·00, root mean square error of approximation (RMSEA) = 0·0001) than the poorly fitting alternative model 2 ($\chi^2 = 34·51$, df = 10, $P=0·001$, NFI = 0·830, CFI = 0·866, RMSEA = 0·114). Model 2 examined the reverse hypothesis that lower cognitive abilities would lead to higher rates of obesity (again controlling for psychological, lifestyle and other physiological factors). Finally, Akaike's information criterion (AIC), which is widely used to compare non-nested models originating from the same data, was considerably smaller (AIC = 59·61) for model 1 than for model 2 (AIC = 84·10), indicating a better fit of the former. Notably, the smaller R^2 values in model 1 (describing the regression of GAMA on each of the mediators) when compared with model 2 (describing the regression of the somatometric index on the same mediators) is explained by

Table 4. Pearson's correlations between variables examined in the structural equation modelling analyses

	1	2	3	4	5	6	7	8	9
1. Age									
2. Education	−0·08								
3. Somatometric	0·28**	−0·32**							
4. Inflammation	0·08	−0·30**	0·47**						
5. GAMA	−0·23**	0·53**	−0·29**	−0·39**					
6. HOMA-IR	0·05	−0·16*	0·38**	0·26**	−0·06				
7. Adiponectin	0·08	0·20**	−0·24**	−0·13	0·002	−0·28**			
8. Godin	−0·25*	0·14	0·33*	0·22**	0·13	−0·19*	0·02		
9. STAI-T	−0·18*	−0·04	0·09	0·09	−0·11	0·04	−0·06	0·16	
10. BDI-II	−0·20**	−0·09	0·12	0·08	−0·21**	0·007	−0·03	0·17	0·78**

Somatometric, composite indices BMI, waist:hip ratio, and Fat%; Inflammation, composite indices high-sensitivity C-reactive protein, erythrocyte sedimentation rate, and fibrinogen; GAMA, General Ability Measure for Adults (raw score); HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; Godin, leisure-time physical activity; STAI-T, State-Trait Anxiety Inventory; BDI-II, Beck Depression Inventory-II.
Values were significantly different: * $P<0·05$, ** $P<0·01$.

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the stronger direct paths of each physiological/exercise variable with the somatometric variable. It is further expected that these associations will be stronger than the direct effects of the same physiological/exercise variables on the (conceptually more distal) cognitive measure.

To ensure that the dataset possessed adequate power for model testing, the structural model in which GAMA was a function of BDI, inflammation, adiponectin, metabolic profile and Godin's scores, all being a function of somatometrics, was simulated with between-construct paths equal to 0·25, to be on the conservative side. On using a Monte Carlo simulation with 500 replications and sample sizes equal to 180 participants, results pointed to the presence of minimal bias. Specifically, the bias of the χ^2 statistic was equal to zero in terms of probabilities of rejected χ^2 values and the actual estimate on the χ^2 values between the expected mode (with 10 df) and the observed bootstrapped model was equal to 0·140.With an expected RMSEA of 0·059, estimates were equal to 0·067, indicating a bias of 0·008, which was negligible. Lastly, the mean square error of the path estimates ranged between 0·0044 and 0·0079.Thus, all power analysis results corroborated with the premise that 180 participants were sufficient to obtain solutions with valid path estimates and proper rejection rates of the χ^2 statistic.

Discussion

In the present study, we investigated the association between obesity, CLGI and cognitive ability in a community sample of young and middle-aged Greek adults free of any obvious medical or psychiatric diseases and grouped as per their BMI. The results of the present study indicated an inverse association between elevated BMI and cognitive performance (assessed using a test of non-verbal logical reasoning ability and fluid intelligence), confirming previously published reports. More specifically, obese participants exhibited significantly poorer performance compared with age-matched overweight and normal-weight participants. The novel finding of the present study is that obesity-linked CLGI, the principal cause of all metabolic consequences of obesity (insulin resistance, diabetes mellitus, atherosclerosis, etc.), appears to be directly associated with cognitive defects as demonstrated by both group-level analyses and mediated regression models.

It is now increasingly being recognised that the deleterious effects of obesity on cognition arise much earlier than previously thought and are not solely mediated by the commonly observed clinical consequences of obesity, such as hypertension, diabetes and atherosclerosis[45]. Instead, these effects may result from obesity-related early pathophysiological effects on innate immunity[46], which, in turn, directly harm the central nervous system. Indeed, there is evidence derived from animal models suggesting that high-fat diet-induced obesity may result in inflammation-mediated harmful effects on several brain areas, including the neocortex and hippocampus[47,48]. Furthermore, peripheral inflammation due to maternal obesity as a result of high-fat diet can be transferred to offspring's brain, resulting in increased microglial activity in the hippocampus at birth, elevated pro-inflammatory cytokine responses in adulthood, anxiety and spatial learning difficulties[49]. In another study, mice fed a very-high-fat lard diet (60%) presented with weight gain and exhibited areas of brain inflammation associated with poorer performance in a challenging maze task, compared with mice fed a high-fat, Western diet (41% fat), resulting in weight gain but not in brain inflammation[50]. Taken together, these experimental findings suggest that CLGI constitutes a pathway via which obesity causes impaired cognition much earlier and independently of the other obesity-induced co-morbidities.

The medical literature suggests that in addition to the degree of systemic inflammation, obese individuals may differ in other pertinent physiological characteristics as well. A considerable percentage of the adult obese population (up to 20%)[51] appears to be less susceptible to the unfavourable metabolic profile that typically accompanies obesity. 'Metabolically healthy' as opposed to 'metabolically unhealthy' obese individuals have been found to have higher insulin sensitivity levels, no signs of hypertension, normal lipid levels, low TAG levels, and high HDL-cholesterol and adiponectin levels and carry a lower risk for developing type 2 diabetes and CVD[52]. However, it should be noted that metabolically healthy obese individuals are characterised by much lower levels of inflammation compared with other obese individuals[53]. Given the present results on the mediating role of inflammation in obesity-linked cognitive performance decline, it appears reasonable to hypothesise that metabolically healthy obese individuals are less prone to cognitive difficulties compared with metabolically unhealthy obese individuals. To our knowledge, the only study that has addressed this question[54] did not support this hypothesis, failing to find differences between metabolically abnormal and metabolically normal obese participants with regard to a global cognitive score either at baseline or at the 10-year follow-up. However, given that Singh-Manoux *et al.*[54] did not include measures of inflammation, the potential role of low-grade inflammation could not be assessed in this intriguing obesity phenotype. The small size of the present study sample notwithstanding, the group-level analysis results do not support this claim, by failing to differentiate between obese individuals with relatively high insulin resistance levels and those demonstrating a more typical metabolic profile.

The second goal of the present study was to explore the potential role of additional physiological factors, namely insulin resistance (HOMA-IR) and adiponectin production, in obesity-related inflammation possibly affecting cognition. However, bivariate correlations between these parameters and GAMA, somatometric index or inflammation were weak, and including them as mediators in the obesity–inflammation–cognition association did not support this hypothesis. Notably, neither adiponectin nor HOMA-IR accounted for significant variability in GAMA scores, contrary to the claim that adiponectin may assume a protective role in cognitive ability as an insulin sensitiser. Studies investigating the association of adiponectin with cognition are to date limited and controversial, focusing on elderly populations[55–58], and challenge the suggested association of adiponectin with a lower risk of CVD[59–61]. In summary, controversial findings from previous studies and the present study stress the need for further

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systematic investigations of the hypothesised inverse association between adiponectin and obesity-related poor cognitive performance. In this direction, use of high-molecular-weight adiponectin as a better indicator of insulin sensitivity instead of total adiponectin has been proposed[62].

Other factors addressed as potential mediators in our proposed obesity–inflammation–cognition model were symptoms of depression and anxiety. Compromised cognitive function, especially in the areas of sustained attention and mental flexibility, has been identified as a characteristic of clinical and subclinical depression[63,64]. Moreover, elevated levels of stress and anxiety have been linked to impaired performance in cognitive tasks[65] as well as increased body weight[66]. Thus, psychoemotional well-being, as indexed by the absence of symptoms of depression and anxiety, has been implicated as a potential mediator of the obesity–cognition association[67]. However, self-reported levels of such symptoms did not differ among the three BMI groups in the present study, indicating that obesity is associated with reduced cognitive function in a more direct way, at least in the present study sample. This finding is in contrast to at least one previous report linking self-reported levels of negative emotions to cognitive impairments independently of BMI[67]. Nonetheless, participants of that study were heavily obese women (mean BMI 43·2 (SD 3·8) kg/m^2) seeking surgical interventions and, unlike the case in the community-dwelling obese group in the present study (mean BMI 34·22 (SD 3·7) kg/m^2), both their inflammatory and psychoemotional profiles may have been overburdened. Consistent with the null findings of the present study, large cross-sectional studies have also failed to find strong associations between obesity and depression, while it was longitudinal studies that established significant bidirectional links between obesity and depression[68].

It would be interesting to determine whether the magnitude of the purported effect of obesity on cognition varies with BMI. According to this hypothesis, obese individuals are more likely to have suffered the subtle but adverse effects of low-grade inflammation at a greater intensity and for a longer period of time than non-obese individuals, sufficient to incur detectable cognitive impairment. Preliminary moderation analyses performed in the present study sample (using BMI group as a moderator of the obesity–inflammation–cognition association) suggest that these effects may indeed be stronger among obese individuals, but subgroup sizes were relatively small to allow for firm conclusions to be drawn. Notably, the cross-sectional design of the present study does not permit quantification of the inflammation 'history' of participants, necessary to establish critical features of inflammation potentially leading to cognitive decline.

In the long run, persistent through lifetime, obesity-induced CLGI is also destined to coalesce with further inflammatory processes observed in elderly, independently of their earlier weight profile. Indeed, in 2000, Franceschi *et al.*[69] were the first to describe an up-regulation of the inflammatory response in the elderly and coined the term 'inflammaging' to refer to this phenomenon. Inflammaging is now generally recognised as another characteristic of old age as part of the general syndrome of immunosenescence. This up-regulation results in the development of chronic low-grade systemic pro-inflammatory state in the elderly, identical to that due to increased adiposity irrespective of age. As expected, it is characterised by an elevation of the levels of several IL as well as those of the acute-phase proteins produced by the liver in response to inflammatory cytokines such as CRP. Genetic, environmental and age-related factors contribute to the development of inflammaging and include polymorphisms to the promoter regions of cytokines, cytokine receptors and antagonists, age-related decreases in autophagy and of course increased adiposity. Although the present study focused on adults aged <65 (mean age 38·3) years, it is predicted that obesity will contribute to the worsening of inflammaging in the elderly, further affecting 'natural' cognitive decline.

A second important limitation of the present study was that the sample consisted mainly of women, preventing exploration of potential sex differences in the proposed impact of obesity and associated low-grade inflammation on cognitive ability. In the present study sample, however, there was no evidence of an effect of sex on the association between obesity and cognition. Furthermore, cognitive changes during the menstrual cycle were not considered in the analyses[70], although participant recruitment and testing schedules should have ensured random distribution of such effects across BMI groups.

A third limitation of the present study was reliance upon a single measure of cognitive ability, while earlier studies focusing exclusively on the obesity–cognition association have examined it more thoroughly, utilising extensive test batteries that address specific cognitive domains. In this context, it was fortuitous that significant effects of obesity and inflammation were found on a measure designed to assess general cognitive ability in the form of fluid intelligence. The sensitivity of GAMA to the effects of obesity and inflammation is not surprising, however, in view of (a) the very high correlations between GAMA scores and, primarily, performance IQ as measured by comprehensive test batteries[26,28], (b) that adequate performance in this task requires reasoning ability, as well as cognitive flexibility, given the variety of alternating logical problems featured, and (c) that GAMA is a timed task, rendering performance sensitive to individual differences in processing speed. Notably, both cognitive flexibility and processing speed are particularly susceptible to diffuse brain insults.

It should further be noted that other commonly used measures of CLGI, such as pro-inflammatory cytokines (e.g. IL-6), were not explored in the present study in view of extant evidence that elevated CRP content is the most robust marker of CLGI in obesity and insulin resistance[13–15]. The fact that the vast majority of the reports of CLGI in obesity use this marker renders the present data comparable to the published literature[17–20].

Perhaps the most critical weakness of the present study concerns the cross-sectional nature of the data, which rendered them incapable of providing a strong test for the directionality of the obesity–inflammation–cognition association. Cognitive flexibility and logical reasoning ability, which are considered to be among the key components of fluid intelligence, are in principle important determinants of everyday decision making and are probably involved in the

adoption of healthy lifestyle and behaviours (nutritional choices and physical activity)[11,12]. Impairments in such abilities may explain obesity development through poor health choices, while the accumulation of body fat and the ensuing low-grade systemic inflammation may account for further cognitive decline. This hypothetical cycle of events may also explain the long-term failure of common obesity prevention and treatment strategies (information on healthy eating choices and encouragement to perform physical activity and follow appropriate diet)[71]. Although longitudinal evidence is required to clarify this issue, structural modelling of the present cross-sectional dataset provides preliminary support to the notion that obesity adversely affects general cognitive ability through a cascade of physiological events rather than the reverse.

Despite these limitations, we were able to identify cognitive decrements in a carefully screened sample of obese individuals, who were free of other serious medical conditions (e.g. chronic autoimmune or inflammatory diseases) or mental disorders (e.g. depression) and establish a mediating role of CLGI. Bearing in mind that obesity often coexists with other medical conditions (e.g. diabetes, hypertension and sleep apnoea syndrome) known to be independently associated with cognitive deficits, it is expected that in a consecutive, unscreened sample of obese individuals, more severe cognitive deficits would be documented. It should be noted that the incidence of obesity in Greece is rising at an alarming rate both in adults[72] and in children[73] in a country that until recently has followed a beneficial-for-weight-control Mediterranean diet, raising concerns regarding obesity-related cognitive dysfunction in this population.

Acknowledgements

The present study was co-funded by the European Union (European Social Fund – ESF) and Greek national funds through the Operational Program 'Education and Lifelong Learning' of the National Strategic Reference Framework (NSRF) – Research Funding Program: Heracleitus II: Investing in knowledge society through the European Social Fund (MIS: 349309. URL: http://www.edulll.gr/). The funding agency had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors' contributions are as follows: E. C. S., P. S. and A. N. M. designed the study; E. C. S., P. D. A., E. D. and M. V. collected the data; E. C. S. and P. S. analysed the data; E. C. S., P. S., A. N. M. and A. N. B. wrote the article.

None of the authors has any conflicts of interest to declare.

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Abbreviations

AD	Alzheimer's Disease
ADHD	Attention Deficit Hyperactivity Disorder
AIC	Akaike's Information Criterion
BAT	Brown Adipose Tissue
BDI-II	Beck Depression Inventory revised edition
BF%	total Body Fat Percentage
BMI	Body Mass Index
BP	Blood Pressure
CFI	Comparative Fit Index
CI	Confidence Interval
CLGI	Chronic Low Grade Inflammation
CVD	Cardio Vascular Disease
DEXA	dual energy X-ray absorptiometry
DMT2	Diabetes Mellitus Type 2
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
EFs	Executive Functions
ESR	Erythrocyte Sedimentation Rate
g	general intelligence
GAMA	General Ability Measure for Adults
Gc	crystallized intelligence
Gf	fluid intelligence
Godin	Godin's leisure-time physical activity questionnaire
HbA1c	Glycosylated Hemoglobin Index
HDL	High-Density Lipoprotein
HOMA-IR	Homeostasis Model Assessment Insulin Resistance index
hs-CRP	high sensitive C-Reactive Protein
IL-6	Interleukin 6
IQ	Intelligence Quotient
LDL	Low-Density Lipoprotein
LPS	Lipopolysaccharide
MCI	Mild Cognitive Impairment
MetS	Metabolic Syndrome
METs	Metabolic Equivalents
NAFLD	Non Alcoholic Fatty Liver Disease
NASH	Non Alcoholic Steatohepatitis
NFI	Normed Fit Index
NFκB	Nuclear factor kappa B
OECD	Organization for Economic Co-operation and Development
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
RMSEA	Root Mean Square Error of Approximation

SEM	Structural Equation Modelling
SES	Socio- Economic Status
STAI-T	Spielberger State–Trait Anxiety Inventory: Trait subscale
TLR	Toll-like receptor
TNF-α	Tumor Necrosis Factor α
VaD	Vascular Dementia
WAIS	Wechsler Adult Intelligence Scale
WaistC	Waist Circumference
WAT	White Adipose Tissue
WHO	World Health Organization
WHR	Waist to Hip Ratio
MHO	“Metabolically Healthy” Obese
MUHO	“Metabolically Unhealthy” Obese
BBB	Blood Brain Barrier
CNS	Central Nervous System

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